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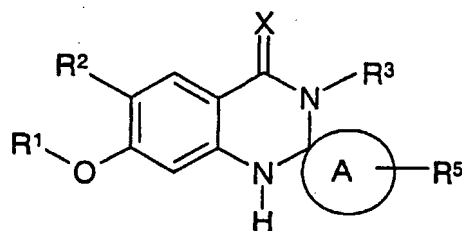
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(54) Title: QUINAZOLINONE DERIVATIVES



(I)

(57) Abstract: A compound of formula (1), wherein: X is an oxygen or sulfur atom; R<sup>1</sup> is an aliphatic, cycloaliphatic or cycloalkyl-alkyl- group; R<sup>2</sup> is an optionally substituted heteroaromatic group or a -CN group; R<sup>3</sup> is a group -(Alk<sup>1</sup>)<sub>m</sub>L<sup>1</sup>(Alk<sup>2</sup>)<sub>n</sub>R<sup>4</sup> in which m and n, which may be the same or different, is each zero or the integer 1, Alk<sup>1</sup> and Alk<sup>2</sup>, which may be the same or different, is each an optionally substituted aliphatic or heteroaliphatic chain, L<sup>1</sup> is a covalent bond or a linker atom or group and R<sup>4</sup> is a hydrogen atom or an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group; A is an optionally substituted cycloaliphatic or heterocycloaliphatic group optionally fused to an optionally substituted aryl or heteroaryl group; R<sup>5</sup>, which may be attached to any available C or N atom present in the cycloaliphatic or heterocycloaliphatic, or where fused, aryl or heteroaryl group, is a group -(Alk<sup>3</sup>)<sub>t</sub>L<sup>2</sup>(Alk<sup>4</sup>)<sub>v</sub>R<sup>6</sup> in which t and v, which may be the same or different, is each zero or the integer 1, Alk<sup>3</sup> and Alk<sup>4</sup>, which may be the same or different, is each an optionally substituted aliphatic or heteroaliphatic chain, L<sup>2</sup> is a covalent bond or a linker atom or group and R<sup>6</sup> is a hydrogen or halogen atom or a -CN group or an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group; and the salts, solvates, hydrates, tautomers, isomers or N-oxides thereof. The compounds of the present invention are potent inhibitors of IMPDH.



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## QUINAZOLINONE DERIVATIVES

This invention relates to a series of quinazolinones and quinazolinthiones and their derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medicine.

Inosine-5'-monophosphate dehydrogenase (IMPDH; EC 1.1.1.205) is an enzyme involved in the *de novo* synthesis of guanine nucleotides. IMPDH catalyses the  $\beta$ -nicotinamide adenine dinucleotide (NAD)-dependant oxidation of inosine-5'-monophosphate (IMP) to xanthosine-5'-monophosphate (XMP) (Jackson R.C. et al., Nature, 256, pp. 331-333, (1975)). Guanine nucleotides are essential to the cell for RNA and DNA synthesis, intermediates in signalling pathways and as energy sources for metabolic pathways.

IMPDH is ubiquitous in eukaryotes, bacteria and protozoa (Y. Natsumeda & S.F. Carr, Ann. N.Y. Acad., 696, pp. 88-93, (1993) ). Two isoforms of human IMPDH, designated type I and type II, have been identified and sequenced (F.R. Collart and E. Huberman, J. Biol. Chem., 263, pp. 15769-15772, (1988); Y. Natsumeda et al J. Biol. Chem., 265, pp 5292-5295, (1990)). Each is 514 amino acids and they share 84% sequence identity. Both IMPDH type I and type II form active tetramers in solution, with subunit molecular weights of 56 kDa (Y. Yamada et. Al., Biochemistry, 27, pp. 2737-2745, (1988) ). It is thought that type I is the predominant isoform expressed in normal cells, whilst type II is upregulated in neoplastic and replicating cells. Studies have postulated that selective inhibition of type II IMPDH could provide a therapeutic advantage by reducing potential toxicity effects caused by inhibiting the type I isoform (Pankiewicz K.W, Expert Opin. Ther. Patents 11 (7) pp 1161-1170, (2001)).

The *de novo* synthesis of guanine nucleotides, and thus the activity of IMPDH, is particularly important in B and T-lymphocytes. These cells depend on the *de novo*, rather than the salvage pathway to generate sufficient levels of nucleotides necessary to initiate a proliferative response to mitogen or antigen

(A.C. Allison et. al., Lancet II, 1179, (1975) and A.C. Allison et. al., Ciba Found. Symp., 48, 207, (1977) ). Thus, IMPDH is an attractive target for selectively inhibiting the immune system without also inhibiting the proliferation of other cells.

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Mycophenolic acid (MPA) and some of its derivatives have been described in United States patents 5,380,879 and 5,444,072 and PCT publications WO 94/01105 and WO 94/12184 as potent, uncompetitive, reversible inhibitors of human IMPDH type I ( $K_i = 33$  nM) and type II ( $K_i = 9$  nM). MPA has been  
10 demonstrated to block the response of B and T-cells to mitogen or antigen (A.C. Allison et. al., Ann. N. Y. Acad. Sci., 696, 63, (1993) ).

Immunosuppressants, such as MPA, are useful drugs in the treatment of transplant rejection and autoimmune diseases. (R.E. Morris, Kidney Intl., 49,  
15 Suppl. 53, S-26, (1996) ). However, MPA is characterized by undesirable pharmacological properties, such as gastrointestinal toxicity. (L.M. Shaw, et. al., Therapeutic Drug Monitoring, 17, pp. 690-699, (1995) ).

Mycophenolate mofetil, a prodrug which quickly liberates free MPA *in vivo*,  
20 was recently approved to prevent acute allograft rejection following kidney transplantation (i.e. renal allograft failure) and heart transplantation. (L.M. Shaw, et. al., Therapeutic Drug Monitoring, 17, pp. 690-699, (1995); H.W. Sollinger, Transplantation, 60, pp. 225-232, (1995); J. Kobashigawa Transplant, 66, pp. 507, (1998) ). Mycophenolate mofetil has also been used  
25 for the treatment of rheumatoid arthritis. The experimental use of mycophenolate mofetil in the treatment of systemic lupus erythematosus, lupus nephritis, myasthenia gravis, inflammatory eye disease, autoimmune and inflammatory skin disorders (including psoriasis) and glomerular disease has also been described (R. Bentley, Chem. Rev., 100, pp. 3801-3825,  
30 (2000)). Mycophenolate mofetil has also been postulated to be of use for the treatment of atopic dermatitis (Grundmann-Kollman M et al, Archives of Dermatology, 137 (7), pp. 870-873, (2001) ) and has been shown to be effective in predictive animal models of multiple sclerosis (Tran G.T et al, International Immunopharmacology, 1 (9-10) pp. 1709-1723, (2001) ).

Several clinical observations, however, limit the therapeutic potential of this drug. (L.M. Shaw, et. al., Therapeutic Drug Monitoring, 17, pp. 690-699, (1995)).

5 Nucleoside analogues such as tiazofurin, ribavirin and mizoribine also inhibit IMPDH (L. Hedstrom, et. al., Biochemistry, 29, pp. 849-854, (1990) ). These nucleoside analogues are competitive inhibitors of IMPDH, but also inhibit other NAD dependant enzymes. This lack of specificity limits the therapeutic application of these compounds. New agents with improved selectivity for  
10 IMPDH would represent a significant improvement over these nucleoside analogues. Mizoribine (Bredinin®) has been approved in Japan for multiple indications in transplantation and autoimmune diseases including prevention of rejection after renal transplantation, idiopathic glomerulonephritis, lupus nephritis and rheumatoid arthritis.

15

Vertex has recently disclosed a series of novel IMPDH inhibitors (WO 97/40028), of which VX-497 has been evaluated for the treatment of psoriasis.

It is also known that IMPDH plays a role in other metabolic events. Increased  
20 IMPDH activity has been observed in rapidly proliferating human leukemic cell lines and other tumour cell lines, indicating IMPDH as a target for anti-cancer as well as immunosuppressive chemotherapy (M. Nagai et. al., Cancer Res., 51, pp. 3886-3890, (1991), Pankiewicz K.W., Exp. Opin. Ther. Patents, 11, pp. 1161-1170, (2001) ). IMPDH has also been shown to play a role in the  
25 proliferation of smooth muscle cells, indicating that inhibitors of IMPDH may be useful in preventing restenosis or other hyperproliferative vascular diseases (C.R. Gregory et. al., Transplantation, 59, pp. 655-61, (1995); PCT publication WO 94/12184; and PCT publication WO 94/ 01105).

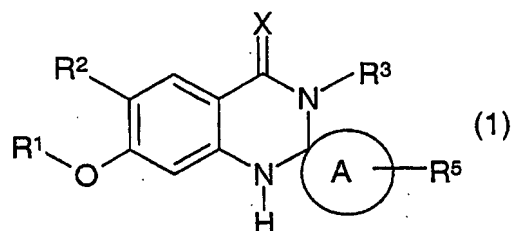
30 Additionally, IMPDH has been shown to play a role in viral replication in some virus-infected cell lines. (S.F. Carr, J. Biol. Chem., 268, pp. 27286-27290, (1993) ). VX-497 is currently being evaluated for the treatment of hepatitis C in humans.

Thus, there remains a need for potent IMPDH inhibitors with improved pharmacological properties. Such inhibitors would have therapeutic potential as immunosuppressants, anti-cancer agents, anti-inflammatory agents, antipsoriatic and anti-viral agents.

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The present inventors disclose a class of substituted quinazolinone and quinazolinthione derivatives having activity as IMPDH inhibitors, and to compositions and methods related thereto.

10 Thus we provide a compound of formula (1):



wherein:

X is an oxygen or sulfur atom;

15 R<sup>1</sup> is an aliphatic, cycloaliphatic or cycloalkyl-alkyl- group;

R<sup>2</sup> is an optionally substituted heteroaromatic group or a -CN group;

R<sup>3</sup> is a group  $-(Alk^1)_m L^1 (Alk^2)_n R^4$  in which m and n, which may be the same or different, is each zero or the integer 1, Alk<sup>1</sup> and Alk<sup>2</sup>, which may be the same or different, is each an optionally substituted aliphatic or heteroaliphatic chain,

20 L<sup>1</sup> is a covalent bond or a linker atom or group and R<sup>4</sup> is a hydrogen atom or an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group;

A is an optionally substituted cycloaliphatic or heterocycloaliphatic group optionally fused to an optionally substituted aryl or heteroaryl group;

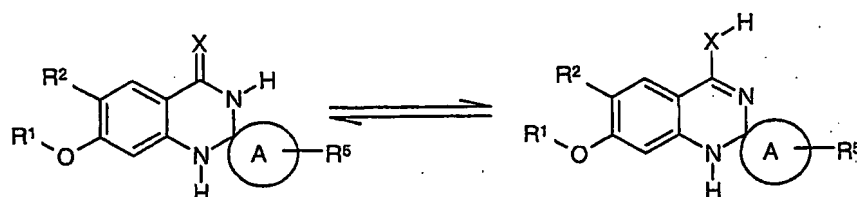
25 R<sup>5</sup>, which may be attached to any available C or N atom present in the cycloaliphatic or heterocycloaliphatic, or where fused, aryl or heteroaryl group, is a group  $-(Alk^3)_t L^2 (Alk^4)_v R^6$  in which t and v, which may be the same or different, is each zero or the integer 1, Alk<sup>3</sup> and Alk<sup>4</sup>, which may be the same or different, is each an optionally substituted aliphatic or heteroaliphatic chain,

30 L<sup>2</sup> is a covalent bond or a linker atom or group and R<sup>6</sup> is a hydrogen or

halogen atom or a -CN group or an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group;  
and the salts, solvates, hydrates, tautomers, isomers or N-oxides thereof.

- 5 It will be appreciated that the ring A and the rest of the molecule of formula (1) are in a spiro relationship to each other.

It will be appreciated that certain compounds of formula (1) may exist as geometric isomers (E or Z isomers). The compounds may also have one or  
10 more chiral centres, and exist as enantiomers or diastereomers. The invention is to be understood to extend to all such geometric isomers, enantiomers, diastereomers and mixtures thereof, including racemates. Formula (1) and the formulae hereinafter are intended to represent all individual isomers and mixtures thereof, unless stated or shown otherwise. In addition, compounds of  
15 formula (1) may exist as tautomers, for example keto ( $\text{CH}_2\text{C}=\text{O}$ ) – enol ( $\text{CH}=\text{CHOH}$ ) tautomers. Quinazolinones may also exist as tautomers; one possible example is illustrated below:



- Formula (1) and the formulae hereinafter are intended to represent all  
20 individual tautomers and mixtures thereof, unless stated otherwise.

It will also be appreciated that where desired the compounds of the invention may be administered in a pharmaceutically acceptable pro-drug form, for example, as a protected carboxylic acid derivative, e.g. as an acceptable  
25 ester. It will be further appreciated that the pro-drugs may be converted *in vivo* to the active compounds of formula (1), and the invention is intended to extend to such pro-drugs. Such prodrugs are well known in the literature, see for example International Patent Application No. WO 00/23419, Bodor N. (Alfred Benson Symposium, 1982, 17, 156-177), Singh G. *et al* (J. Sci. Ind.

Res., 1996, 55, 497-510) and Bundgaard H. (Design of Prodrugs, 1985, Elsevier, Amsterdam).

In the compounds of the invention as represented by formula (1) and the more  
 5 detailed description hereinafter certain of the general terms used in relation to  
 substituents are to be understood to include the following atoms or groups  
 unless specified otherwise.

The term "aliphatic group" is intended to include optionally substituted straight  
 10 or branched C<sub>1-10</sub>alkyl, e.g. C<sub>1-6</sub> alkyl, C<sub>2-10</sub>alkenyl e.g. C<sub>2-6</sub>alkenyl or C<sub>2-10</sub>  
 alkynyl e.g. C<sub>2-6</sub>alkynyl groups.

Particular examples of aliphatic groups include optionally substituted straight  
 or branched C<sub>1-6</sub> alkyl groups such as -CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>3</sub>, -CH(CH<sub>3</sub>)<sub>2</sub>,  
 15 -(CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>, -(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>, -CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, -CH<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>,  
 -C(CH<sub>3</sub>)<sub>3</sub>, -(CH<sub>2</sub>)<sub>4</sub>CH<sub>3</sub>, -(CH<sub>2</sub>)<sub>5</sub>CH<sub>3</sub>, or C<sub>2-6</sub>alkenyl or C<sub>2-6</sub>alkynyl groups such  
 as -CHCH<sub>2</sub>, -CHCHCH<sub>3</sub>, -CH<sub>2</sub>CHCH<sub>2</sub>, -CHCHCH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CHCHCH<sub>3</sub>,  
 -(CH<sub>2</sub>)<sub>2</sub>CHCH<sub>2</sub>, -CCH, -CCCH<sub>3</sub>, -CH<sub>2</sub>CCH, -CCCH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CCCH<sub>3</sub>, or  
 -(CH<sub>2</sub>)<sub>2</sub>CCH groups. More particular examples include optionally substituted  
 20 C<sub>1-4</sub> alkyl groups selected from -CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>3</sub>, -CH(CH<sub>3</sub>)<sub>2</sub>, -(CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>,  
 -CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, -(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub> or -C(CH<sub>3</sub>)<sub>3</sub>.

The term "aliphatic chain" is intended to include those alkyl, alkenyl or alkynyl  
 groups as just described where a terminal hydrogen atom is replaced by a  
 25 covalent bond to give a divalent chain.

Examples of aliphatic chains include optionally substituted straight or branched  
 C<sub>1-6</sub> alkylene chains such as -CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>-, -CH(CH<sub>3</sub>)CH<sub>2</sub>-, -(CH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub>-,  
 -(CH<sub>2</sub>)<sub>3</sub>CH<sub>2</sub>-, -CH(CH<sub>3</sub>)(CH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH(CH<sub>3</sub>)CH<sub>2</sub>-, -C(CH<sub>3</sub>)<sub>2</sub>-,  
 30 -C(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>-, -(CH<sub>2</sub>)<sub>2</sub>CH(CH<sub>3</sub>)CH<sub>2</sub>-, -CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>-,  
 -CH(CH<sub>3</sub>)CH<sub>2</sub>CH(CH<sub>3</sub>)CH<sub>2</sub>-, -CH<sub>2</sub>CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>-, -(CH<sub>2</sub>)<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>-,  
 -(CH<sub>2</sub>)<sub>4</sub>CH<sub>2</sub>-, -(CH<sub>2</sub>)<sub>5</sub>CH<sub>2</sub> or C<sub>2-6</sub>alkenylene or C<sub>2-6</sub>alkynylene chains such as  
 -CHCH-, -CHCHCH<sub>2</sub>-, -CH<sub>2</sub>CHCH-, -CHCHCH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CHCHCH<sub>2</sub>-,



-(CH<sub>2</sub>)<sub>2</sub>CHCH-, -CC-, -CCCH<sub>2</sub>-, -CH<sub>2</sub>CC-, -CCCH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CCCH<sub>2</sub>- or -(CH<sub>2</sub>)<sub>2</sub>CCH- chains. More particular examples include optionally substituted C<sub>1-3</sub> alkylene chains selected from -CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, -CH(CH<sub>3</sub>)CH<sub>2</sub>-, -C(CH<sub>3</sub>)<sub>2</sub>- and -CH<sub>2</sub>CH(CH<sub>3</sub>)- chains.

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Optional substituents that may be present on the aliphatic groups or chains include those optional substituents mentioned hereinafter.

The term "heteroaliphatic chain" is intended to include the aliphatic chains just described but with each additionally containing one, two, three or four heteroatoms or heteroatom-containing groups. Particular heteroatoms or groups include atoms or groups L<sup>3</sup> where L<sup>3</sup> is a linker atom or group. Each L<sup>3</sup> atom or group may interrupt the aliphatic group, or may be positioned at its terminal carbon atom to connect the group to an adjoining atom or group. Particular examples include optionally substituted -L<sup>3</sup>CH<sub>2</sub>-, -CH<sub>2</sub>L<sup>3</sup>-, -L<sup>3</sup>CH(CH<sub>3</sub>)-, -CH(CH<sub>3</sub>)L<sup>3</sup>-, -CH<sub>2</sub>L<sup>3</sup>CH<sub>2</sub>-, -L<sup>3</sup>CH<sub>2</sub>CH<sub>2</sub>-, -L<sup>3</sup>CH<sub>2</sub>CH(CH<sub>3</sub>)-, -CH(CH<sub>3</sub>)CH<sub>2</sub>L<sup>3</sup>-, -CH<sub>2</sub>CH<sub>2</sub>L<sup>3</sup>-, -CH<sub>2</sub>L<sup>3</sup>CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>L<sup>3</sup>CH<sub>2</sub>CH<sub>2</sub>L<sup>3</sup>-, -(CH<sub>2</sub>)<sub>2</sub>L<sup>3</sup>CH<sub>2</sub>-, -(CH<sub>2</sub>)<sub>3</sub>L<sup>3</sup>CH<sub>2</sub>-, -L<sup>3</sup>(CH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub>-, -L<sup>3</sup>CH<sub>2</sub>CHCH-, -CHCHCH<sub>2</sub>L<sup>3</sup>-, -(CH<sub>2</sub>)<sub>2</sub>L<sup>3</sup>CH<sub>2</sub>CH<sub>2</sub>-, -(CH<sub>2</sub>)<sub>3</sub>L<sup>3</sup>- and -L<sup>3</sup>CH<sub>2</sub>L<sup>3</sup>CH<sub>2</sub>CH<sub>2</sub>- chains.

20

When L<sup>3</sup> is present in heteroaliphatic chains as a linker atom or group it may be any divalent linking atom or group. Particular examples include -O- or -S- atoms or -C(O)-, -C(S)-, -S(O)-, -S(O)<sub>2</sub>-, -C(O)O-, -OC(O)-, -N(R<sup>7</sup>)- [where R<sup>7</sup> is a hydrogen atom or a straight or branched C<sub>1-6</sub>alkyl group], -N(R<sup>7</sup>)O-, -N(R<sup>7</sup>)N-, -CON(R<sup>7</sup>)-, -OC(O)N(R<sup>7</sup>)-, -CSN(R<sup>7</sup>)-, -N(R<sup>7</sup>)CO-, -N(R<sup>7</sup>)C(O)O-, -N(R<sup>7</sup>)CS-, -S(O)<sub>2</sub>N(R<sup>7</sup>)-, -N(R<sup>7</sup>)S(O)<sub>2</sub>-, -N(R<sup>7</sup>)CON(R<sup>7</sup>)-, -N(R<sup>7</sup>)CSN(R<sup>7</sup>), -N(R<sup>7</sup>)SO<sub>2</sub>N(R<sup>7</sup>)-, -C(=NOR<sup>7</sup>)- or -C(R<sup>8</sup>)=NO- [where R<sup>8</sup> is a straight or branched C<sub>1-6</sub>alkyl group] groups. Where L<sup>3</sup> contains two R<sup>7</sup> groups these may be the same or different.

30

The term "cycloaliphatic group" includes optionally substituted non-aromatic cyclic or multicyclic, saturated or partially saturated C<sub>3-10</sub> ring systems, such as, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl,

adamantyl, norbornyl, norbornenyl, bicyclo[2.2.1]heptanyl or bicyclo[2.2.1]heptenyl. Particular examples include optionally substituted C<sub>3-6</sub> cycloalkyl ring systems such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups. Optional substituents present on those groups include  
 5 those substituents mentioned hereinafter.

The term "cycloalkyl-alkyl- group" refers to a C<sub>1-6</sub> alkyl group (as described herein) where a terminal hydrogen atom is replaced by a C<sub>3-6</sub> cycloalkyl ring (as described herein). Examples include -(CH<sub>2</sub>)<sub>1-6</sub>-cyclopropyl, -(CH<sub>2</sub>)<sub>1-6</sub>-cyclobutyl, -(CH<sub>2</sub>)<sub>1-6</sub>-cyclopentyl or -(CH<sub>2</sub>)<sub>1-6</sub>-cyclohexyl.  
 10

The term "heterocycloaliphatic group" refers to an optionally substituted 3 to 10 membered saturated or partially saturated monocyclic or multicyclic hydrocarbon ring system containing one, two, three or four L<sup>4</sup> linker atoms or groups. Particular examples of suitable L<sup>4</sup> atoms or groups include -O- or -S-  
 15 atoms or -C(O)-, -C(O)O-, -OC(O)-, -C(S)-, -S(O)-, -S(O)<sub>2</sub>-, -N(R<sup>7</sup>)- [where R<sup>7</sup> is as defined above], -N(R<sup>7</sup>)N(R<sup>7</sup>), -N(R<sup>7</sup>)O-, -ON(R<sup>7</sup>)-, -CON(R<sup>7</sup>)-, -OC(O)N(R<sup>7</sup>)-, -CSN(R<sup>7</sup>)-, -N(R<sup>7</sup>)CO-, -N(R<sup>7</sup>)C(O)O-, -N(R<sup>7</sup>)CS-, -S(O)<sub>2</sub>N(R<sup>7</sup>), -N(R<sup>7</sup>)S(O)<sub>2</sub>-, -N(R<sup>7</sup>)CON(R<sup>7</sup>)-, -N(R<sup>7</sup>)CSN(R<sup>7</sup>)-, -N(R<sup>7</sup>)SO<sub>2</sub>N(R<sup>7</sup>)- groups.  
 20 Where the linker group contains two R<sup>7</sup> substituents, these may be the same or different. Optional substituents present on the heterocycloaliphatic groups include those substituents mentioned hereinafter.

Particular examples of heterocycloaliphatic groups include optionally  
 25 substituted cyclobutanonyl, cyclopentanonyl, cyclohexanonyl, azetidiny, tetrahydrofuranyl, tetrahydropyranyl, pyrrolinyl, e.g. 2- or 3-pyrrolinyl, pyrrolidinyl, pyrrolidinonyl, oxazolidinyl, oxazolidinonyl, dioxolanyl, e.g. 1,3-dioxolanyl, imidazolinyl, e.g. 2-imidazolinyl, imidazolidinyl, imidazolidinonyl, imidazolidine-2,4-dionyl, pyrazolinyl, e.g. 2-pyrazolinyl, pyrazolidinyl, thiazolinyl, thiazolidinyl, pyranyl, e.g. 2- or 4-pyranyl, pyranonyl, piperidinyl,  
 30 piperidinonyl, quinuclidinyl, 1,4-dioxanyl, morpholinyl, morpholinonyl, 1,4-dithianyl, thiomorpholinyl, piperazinyl, N-C<sub>1-6</sub> alkylpiperazinyl, N-C<sub>1-6</sub> alkylpyrrolidinyl, N-C<sub>1-6</sub> alkylpiperidinyl, N-C<sub>1-6</sub> alkylmorpholinyl,

homopiperazinyl, dihydrofuran-2-onyl, tetrahydropyran-2-onyl, isothiazolidinyl  
 1,1-dioxide, [1,2]thiazinanyl 1,1-dioxide, tetrahydrothiophenyl,  
 tetrahydrothiopyranyl, pyrazolidin-3-onyl, tetrahydrothiopyranyl 1,1-dioxide,  
 tetrahydrothiophenyl 1,1-dioxide, 1,3,5-trithianyl, oxazinyl, e.g. 2*H*-1,3-, 6*H*-  
 5 1,3-, 6*H*-1,2-, 2*H*-1,2- or 4*H*-1,4- oxazinyl, 1,2,5-oxathiazinyl, isoxazinyl, e.g.  
 o- or p-isoxazinyl, oxathiazinyl, e.g. 1,2,5 or 1,2,6-oxathiazinyl, 1,3,5-  
 oxadiazinyl or tetrahydropyrrolo[1,2-*c*]imidazole-1,3-dionyl groups.

Cycloaliphatic groups may be linked to the remainder of the compound of  
 10 formula (1) by any available ring carbon atom. Heterocycloaliphatic groups  
 may be linked to the remainder of the compound of formula (1) by any  
 available ring carbon or, where available, ring nitrogen atom.

The optional substituents which may be present on the aliphatic, cycloaliphatic  
 15 or heterocycloaliphatic groups, include one, two, three or more substituents,  
 which each may be the same or different, selected from halogen atoms, or C<sub>1-6</sub>  
 alkyl, e.g. methyl, ethyl, propyl or *i*-propyl, C<sub>1-6</sub>alkoxy, e.g. methoxy, ethoxy or  
 propoxy, haloC<sub>1-6</sub>alkyl, e.g. halomethyl or haloethyl such as difluoromethyl or  
 trifluoromethyl, haloC<sub>1-6</sub>alkoxy, e.g. halomethoxy or haloethoxy such as  
 20 difluoromethoxy or trifluoromethoxy, C<sub>1-6</sub>alkylthio, e.g. methylthio, ethylthio or  
 propylthio, or -(Alk<sup>5</sup>)<sub>g</sub>R<sup>9</sup> groups in which Alk<sup>5</sup> is a straight or branched C<sub>1-3</sub>  
 alkylene chain, *g* is zero or the integer 1 and R<sup>9</sup> is a -OH, -SH, -N(R<sup>10</sup>)<sub>2</sub>  
 [where R<sup>10</sup> is a hydrogen atom or an optionally substituted C<sub>1-6</sub>alkyl group],  
 -CN, -CO<sub>2</sub>R<sup>10</sup>, -OC(O)R<sup>10</sup>, -NO<sub>2</sub>, -C(O)N(R<sup>10</sup>)<sub>2</sub>, -C(S)N(R<sup>10</sup>)<sub>2</sub>, -C(O)R<sup>10</sup>,  
 25 -C(S)R<sup>10</sup>, -N(R<sup>10</sup>)C(O)R<sup>10</sup>, -N(R<sup>10</sup>)C(S)(R<sup>10</sup>), -SO<sub>2</sub>N(R<sup>10</sup>)<sub>2</sub>, -N(R<sup>10</sup>)SO<sub>2</sub>R<sup>10</sup>,  
 N(R<sup>10</sup>)C(O)N(R<sup>10</sup>)<sub>2</sub>, N(R<sup>10</sup>)C(S)N(R<sup>10</sup>)<sub>2</sub>, N(R<sup>10</sup>)SO<sub>2</sub>N(R<sup>10</sup>)<sub>2</sub>, -SO<sub>2</sub>R<sup>10</sup>,  
 -SO<sub>3</sub>R<sup>10</sup>, -OCO<sub>2</sub>R<sup>10</sup>, -OC(O)N(R<sup>10</sup>)<sub>2</sub> or an optionally substituted aromatic or  
 heteroaromatic group. R<sup>9</sup> may also be an -OR<sup>9a</sup> group [where R<sup>9a</sup> is an  
 optionally substituted C<sub>1-6</sub>alkyl, phenyl or 5 or 6 membered heteroaryl group].  
 30 When two R<sup>10</sup> atoms or groups are present in these substituents these may  
 be the same or different or joined to form a heterocycloaliphatic ring which  
 contains at least one N atom. This includes, for example, azetidiny, pyrrolidinyl,  
 piperidinyl, imidazolidinyl, thiazolidinyl, pyrazolidinyl, piperazinyl,

N-C<sub>1-6</sub> alkylpiperazinyl, homopiperazinyl, morpholinyl, thiomorpholinyl, oxazolidinyl and the like. The aromatic and heteroaromatic groups which may be present in these substituents may optionally be substituted by one, two or three of the R<sup>12</sup> groups described herein.

5

The optional substituents which may be present on aliphatic or heteroaliphatic chains, for example Alk<sup>1</sup>, Alk<sup>2</sup>, Alk<sup>3</sup> or Alk<sup>4</sup>, include one, two, three or more substituents where each substituent may be the same or different and is selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or -OH, CN, -CO<sub>2</sub>H, -CO<sub>2</sub>R<sup>11</sup> [where R<sup>11</sup> is an optionally substituted C<sub>1-6</sub>alkyl group] e.g. -CO<sub>2</sub>CH<sub>3</sub> or -CO<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>; -CONHR<sup>11</sup>, e.g. -CONHCH<sub>3</sub>; -CON(R<sup>11</sup>)<sub>2</sub>, e.g. -CON(CH<sub>3</sub>)<sub>2</sub>; -COR<sup>11</sup>, e.g. -COCH<sub>3</sub>; C<sub>1-6</sub>alkoxy, e.g. methoxy or ethoxy; haloC<sub>1-6</sub>alkoxy, e.g. trifluoromethoxy or difluoromethoxy; -SH, -S(O)R<sup>11</sup>, e.g. -S(O)CH<sub>3</sub>; -S(O)<sub>2</sub>R<sup>11</sup>, e.g. -S(O)<sub>2</sub>CH<sub>3</sub>; C<sub>1-6</sub>alkylthio e.g. methylthio or ethylthio; amino; -NHR<sup>11</sup>, e.g. -NHCH<sub>3</sub> or -N(R<sup>11</sup>)<sub>2</sub>, e.g. -N(CH<sub>3</sub>)<sub>2</sub> groups. Where two R<sup>11</sup> groups are present in any of the above substituents these may be the same or different.

When R<sup>9a</sup>, R<sup>10</sup> or R<sup>11</sup> is present as a straight or branched C<sub>1-6</sub>alkyl group it may be a straight or branched C<sub>1-6</sub> alkyl group e.g. a C<sub>1-3</sub> alkyl group such as methyl, ethyl or *i*-propyl. Optional substituents which may be present on such groups include for example one, two or three substituents which may be the same or different selected from fluorine, chlorine, bromine or iodine atoms or hydroxy or C<sub>1-6</sub> alkoxy e.g. methoxy or ethoxy groups.

25

The term "halogen atom" is intended to include fluorine, chlorine, bromine or iodine atoms.

The term "haloalkyl" is intended to include the alkyl groups just mentioned substituted by one, two or three of the halogen atoms just described. Particular examples of such groups include -CF<sub>3</sub>, -CCl<sub>3</sub>, -CHF<sub>2</sub>, -CHCl<sub>2</sub>, -CH<sub>2</sub>F, and -CH<sub>2</sub>Cl groups.

30

The term "alkoxy" as used herein is intended to include straight or branched C<sub>1-10</sub>alkoxy for example C<sub>1-6</sub>alkoxy such as methoxy, ethoxy, *n*-propoxy, *i*-propoxy and *t*-butoxy. "Haloalkoxy" as used herein includes any of those alkoxy groups substituted by one, two or three halogen atoms as described  
5 above. Particular examples include -OCF<sub>3</sub>, -OCCl<sub>3</sub>, -OCHF<sub>2</sub>, -OCHCl<sub>2</sub>, -OCH<sub>2</sub>F and -OCH<sub>2</sub>Cl groups.

As used herein the term "alkylthio" is intended to include straight or branched C<sub>1-10</sub>alkylthio, e.g. C<sub>1-6</sub>alkylthio such as methylthio or ethylthio groups.

10

When L<sup>1</sup> and L<sup>2</sup> are present in compounds of formula (1) as a linker atom or group they may be any such atom or group as hereinbefore described in relation to L<sup>3</sup> linker atoms and groups. When m in compounds of formula (1) is zero then L<sup>1</sup>, when present, is a -C(O)-, -C(S)-, -S(O)<sub>2</sub>-, -CON(R<sup>7</sup>)-, -CSN(R<sup>7</sup>)- or -S(O)<sub>2</sub>N(R<sup>7</sup>)- group, where R<sup>7</sup> is as herein defined. Additionally  
15 L<sup>2</sup> may also be a -C(O)N(R<sup>7</sup>)C(O)-, -C(O)N(R<sup>7</sup>)C(O)O- or -C(O)N(R<sup>7</sup>)O- linker group.

The terms "aromatic group" and "aryl group" are intended to include for  
20 example optionally substituted monocyclic ring C<sub>6-12</sub> aromatic groups, such as phenyl, or bicyclic fused ring C<sub>6-12</sub> aromatic groups, such as, 1- or 2-naphthyl groups.

The terms "heteroaromatic group" and "heteroaryl group" are intended to  
25 include for example optionally substituted C<sub>1-9</sub> heteroaromatic groups containing for example one, two, three or four heteroatoms selected from oxygen, sulfur or nitrogen atoms (or oxidised versions thereof). In general, the heteroaromatic groups may be for example monocyclic or bicyclic fused ring heteroaromatic groups. Monocyclic heteroaromatic groups include for  
30 example five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulfur or nitrogen atoms. Bicyclic heteroaromatic groups include for example eight- to thirteen-

membered fused-ring heteroaromatic groups containing one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms.

Each of these aromatic or heteroaromatic groups may optionally be substituted by one, two, three or more  $R^{12}$  atoms or groups as defined below.

Particular examples of monocyclic ring heteroaromatic groups of this type include pyrrolyl, furyl, thienyl, imidazolyl, *N*- $C_{1-6}$ alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, tetrazolyl, triazinyl, pyridyl-*N*-oxide, dihydropyrazolonyl or imidazolonyl.

Particular examples of bicyclic ring heteroaromatic groups of this type include benzofuryl, benzothienyl, benzotriazolyl, indolyl, indazolinyl, benzimidazolyl, imidazo[1,2-*a*]pyridyl, benzothiazolyl, benzoxazolyl, benzisoxazolyl, benzopyranyl, quinazolinyl, quinoxalinyl, naphthyridinyl, pyrido[3,4-*b*]pyridyl, pyrido[3,2-*b*]pyridyl, pyrido[4,3-*b*]-pyridyl, quinolinyl, isoquinolinyl or phthalazinyl.

The heteroaromatic groups may be attached to the remainder of the compound of formula (1) by any carbon or hetero e.g. nitrogen atom as appropriate.

Optional substituents which may be present on the aromatic or heteroaromatic groups include one, two, three or more substituents, each selected from an atom or group  $R^{12}$  in which  $R^{12}$  is the group  $-(Alk^6)_e(R^{12a})_f$  in which  $Alk^6$  is a straight or branched  $C_{1-6}$ alkylene,  $C_{2-6}$ alkenylene or  $C_{2-6}$ alkynylene chain, optionally interrupted by one, two or three -O- or -S- atoms or  $-S(O)_g$  [where *g* is an integer 1 or 2] or  $-N(R^{14})$ - groups;  $R^{12a}$  is a halogen atom, or an amino ( $-NH_2$ ),  $-NHR^{13}$  [where  $R^{13}$  is the group  $-(Alk^6)_e(R^{13a})_f$  in which  $R^{13a}$  is an optionally substituted heterocycloaliphatic, cycloaliphatic, aryl, heteroaryl group and  $Alk^6$ , *e* and *f* are as herein defined],  $-N(R^{13})_2$ , nitro, cyano, amidino, formyl, hydroxy (OH), carboxyl ( $-CO_2H$ ),  $-CO_2R^{13}$ , thiol ( $-SH$ ),  $-SR^{13}$ ,  $-OR^{13}$ ,

-COR<sup>13</sup>, -CSR<sup>13</sup>, -SO<sub>3</sub>H, -SOR<sup>13</sup>, -SO<sub>2</sub>R<sup>13</sup>, -SO<sub>3</sub>R<sup>13</sup>, -SO<sub>2</sub>NH<sub>2</sub>, -SO<sub>2</sub>NHR<sup>13</sup>,  
 SO<sub>2</sub>N(R<sup>13</sup>)<sub>2</sub>, -CONH<sub>2</sub>, -CSNH<sub>2</sub>, -CONHR<sup>13</sup>, -CSNHR<sup>13</sup>, -CON(R<sup>13</sup>)<sub>2</sub>,  
 -CSN(R<sup>13</sup>)<sub>2</sub>, -N(R<sup>14</sup>)SO<sub>2</sub>R<sup>13</sup>, [where R<sup>14</sup> is a hydrogen atom or a straight or  
 branched C<sub>1-6</sub> alkyl group] -N(SO<sub>2</sub>R<sup>13</sup>)<sub>2</sub>, -N(R<sup>14</sup>)SO<sub>2</sub>NH<sub>2</sub>, -N(R<sup>14</sup>)SO<sub>2</sub>NHR<sup>13</sup>,  
 5 -N(R<sup>13</sup>)SO<sub>2</sub>N(R<sup>14</sup>)<sub>2</sub>, -N(R<sup>14</sup>)COR<sup>13</sup>, -N(R<sup>14</sup>)CONH<sub>2</sub>, -N(R<sup>14</sup>)CONHR<sup>13</sup>,  
 -N(R<sup>14</sup>)CON(R<sup>13</sup>)<sub>2</sub>, -N(R<sup>14</sup>)CSNH<sub>2</sub>, -N(R<sup>14</sup>)CSNHR<sup>13</sup>, -N(R<sup>14</sup>)CSN(R<sup>13</sup>)<sub>2</sub>,  
 -N(R<sup>14</sup>)CSR<sup>13</sup>, -N(R<sup>14</sup>)C(O)OR<sup>13</sup>, -SO<sub>2</sub>NHet<sup>1</sup> [where -NHet<sup>1</sup> is an optionally  
 substituted C<sub>3-7</sub> heterocycloaliphatic group optionally containing one or more  
 other -O- or -S- atoms or -N(R<sup>14</sup>)-, -C(O)- or -C(S)- groups], -CONHet<sup>1</sup>,  
 10 -CSNHet<sup>1</sup>, -N(R<sup>14</sup>)SO<sub>2</sub>NHet<sup>1</sup>, -N(R<sup>14</sup>)CONHet<sup>1</sup>, -N(R<sup>14</sup>)CSNHet<sup>1</sup>,  
 -SO<sub>2</sub>N(R<sup>14</sup>)Het<sup>2</sup> [where Het<sup>2</sup> is an optionally substituted monocyclic C<sub>3-7</sub>  
 cycloaliphatic group optionally containing one or more -O- or -S- atoms or  
 -N(R<sup>14</sup>)-, -C(O)- or -C(S)- groups], -CON(R<sup>14</sup>)Het<sup>2</sup>, -CSN(R<sup>14</sup>)Het<sup>2</sup>,  
 -N(R<sup>14</sup>)CON(R<sup>14</sup>)Het<sup>2</sup>, -N(R<sup>14</sup>)CSN(R<sup>14</sup>)Het<sup>2</sup>, optionally substituted aryl,  
 15 heteroaryl, cycloaliphatic or heterocycloaliphatic group; e is zero or the integer  
 1 and f is zero or an integer 1, 2 or 3; provided that when e is zero then f is the  
 integer 1. It will be further appreciated that when two R<sup>13</sup> or R<sup>14</sup> groups are  
 present in one of the above substituents, the R<sup>13</sup> or R<sup>14</sup> groups may be the  
 same or different.

20

When in the group -(Alk<sup>6</sup>)<sub>e</sub>(R<sup>12a</sup>)<sub>f</sub> or -(Alk<sup>6</sup>)<sub>e</sub>(R<sup>13a</sup>)<sub>f</sub> f is an integer 1, 2 or 3 and  
 e is the integer 1, it is to be understood that the substituent or substituents  
 R<sup>12a</sup> or R<sup>13a</sup> may be present on any suitable carbon atom in -Alk<sup>6</sup>. Where  
 more than one R<sup>12a</sup> or R<sup>13a</sup> substituent is present these may be the same or  
 25 different and may be present on the same or different atom in -Alk<sup>6</sup>. It will be  
 understood that, when f is zero and no substituent R<sup>12a</sup> or R<sup>13a</sup> is present the  
 chain represented by Alk<sup>6</sup> contains a terminal hydrogen atom and becomes a  
 corresponding group.

30 When -NHet<sup>1</sup> or -Het<sup>2</sup> forms part of a substituent R<sup>12a</sup> each may be for  
 example an optionally substituted 2- or 3-pyrrolinyl, pyrrolidinyl, pyrazolinyl,  
 pyrazolidinyl, piperazinyl, imidazolinyl, imidazolidinyl, morpholinyl,  
 thiomorpholinyl, piperidinyl, oxazolidinyl or thiazolidinyl group. Additionally

Het<sup>2</sup> may represent for example, an optionally substituted cyclopentyl or cyclohexyl group. Optional substituents which may be present on -NHet<sup>1</sup> or -Het<sup>2</sup> include those substituents described above in relation to aromatic groups.

5

Particularly useful atoms or groups represented by R<sup>12</sup> include fluorine, chlorine, bromine or iodine, C<sub>1-6</sub> alkyl, e.g. methyl, ethyl, *i*-propyl, haloC<sub>1-6</sub>alkyl, e.g. -CF<sub>3</sub>, haloC<sub>1-6</sub> alkoxy, e.g. -OCF<sub>3</sub>, -OCF<sub>2</sub>H, -(Alk<sup>6</sup>)<sub>e</sub>NH<sub>2</sub>, -(Alk<sup>6</sup>)<sub>e</sub>NHR<sup>13</sup>, -(Alk<sup>6</sup>)<sub>e</sub>N(R<sup>13</sup>)<sub>2</sub>, -(Alk<sup>6</sup>)<sub>e</sub>CN, -(Alk<sup>6</sup>)<sub>e</sub>CO<sub>2</sub>H, -(Alk<sup>6</sup>)<sub>e</sub>CO<sub>2</sub>R<sup>13</sup>, -(Alk<sup>6</sup>)<sub>e</sub>SR<sup>13</sup>,  
 10 -(Alk<sup>6</sup>)<sub>e</sub>OR<sup>13</sup>, -(Alk<sup>6</sup>)<sub>e</sub>COR<sup>13</sup>, -(Alk<sup>6</sup>)<sub>e</sub>CSR<sup>13</sup>, -(Alk<sup>6</sup>)<sub>e</sub>SO<sub>2</sub>R<sup>13</sup>, -(Alk<sup>6</sup>)<sub>e</sub>SO<sub>2</sub>NH<sub>2</sub>, -(Alk<sup>6</sup>)<sub>e</sub>SO<sub>2</sub>NHR<sup>13</sup>, -(Alk<sup>6</sup>)<sub>e</sub>SO<sub>2</sub>N(R<sup>13</sup>)<sub>2</sub>, -(Alk<sup>6</sup>)<sub>e</sub>CONH<sub>2</sub>, -(Alk<sup>6</sup>)<sub>e</sub>CSNH<sub>2</sub>, -(Alk<sup>6</sup>)<sub>e</sub>CONHR<sup>13</sup>, -(Alk<sup>6</sup>)<sub>e</sub>CSNHR<sup>13</sup>, -(Alk<sup>6</sup>)<sub>e</sub>CON(R<sup>13</sup>)<sub>2</sub>, -(Alk<sup>6</sup>)<sub>e</sub>CSN(R<sup>13</sup>)<sub>2</sub>, -(Alk<sup>6</sup>)<sub>e</sub>N(R<sup>14</sup>)SO<sub>2</sub>R<sup>13</sup>, -(Alk<sup>6</sup>)<sub>e</sub>N(R<sup>14</sup>)COR<sup>13</sup>, -(Alk<sup>6</sup>)<sub>e</sub>N(R<sup>14</sup>)CONH<sub>2</sub>, -(Alk<sup>6</sup>)<sub>e</sub>N(R<sup>14</sup>)CONHR<sup>13</sup>, -(Alk<sup>6</sup>)<sub>e</sub>N(R<sup>14</sup>)CSR<sup>13</sup>, -(Alk<sup>6</sup>)<sub>e</sub>N(R<sup>14</sup>)C(O)OR<sup>13</sup>,  
 15 -(Alk<sup>6</sup>)<sub>e</sub>SO<sub>2</sub>NHet<sup>1</sup>, -(Alk<sup>6</sup>)<sub>e</sub>CONHet<sup>1</sup>, -(Alk<sup>6</sup>)<sub>e</sub>CSNHet<sup>1</sup>, optionally substituted -(Alk<sup>6</sup>)<sub>e</sub>phenyl, -(Alk<sup>6</sup>)<sub>e</sub>monocyclic heteroaryl, -(Alk<sup>6</sup>)<sub>e</sub>monocyclic heterocycloaliphatic or (Alk<sup>6</sup>)<sub>e</sub>cycloaliphatic.

Particularly useful R<sup>13</sup> groups include a C<sub>1-6</sub> alkyl group (where f is zero), or an  
 20 optionally substituted -(Alk<sup>6</sup>)<sub>e</sub>phenyl, -(Alk<sup>6</sup>)<sub>e</sub>monocyclic heteroaryl, -(Alk<sup>6</sup>)<sub>e</sub>monocyclic heterocycloaliphatic or -(Alk<sup>6</sup>)<sub>e</sub>cycloaliphatic.

When Alk<sup>6</sup> is present in the above R<sup>12</sup> and R<sup>13</sup> groups it may be for example a methylene, ethylene, *n*-propylene, *i*-propylene, *n*-butylene, *i*-butylene, *s*-  
 25 butylene, *t*-butylene, ethynylene, 2-propynylene, 2-butenylene, 3-butenylene, ethynylene, 2-propynylene, 2-butynylene or 3-butynylene chain, optionally interrupted by one, two, or three -O- or -S-, atoms or -S(O)-, -S(O)<sub>2</sub>- or -N(R<sup>14</sup>)- groups. Particular examples of Alk<sup>6</sup> include C<sub>1-4</sub> alkylene chains e.g. methylene, ethylene, propylene, *i*-propylene or *t*-butylene.

30

R<sup>13</sup> is most especially a C<sub>1-3</sub> alkyl group. R<sup>14</sup> is particularly hydrogen or methyl.



When, in  $R^{12}$  or  $R^{13}$ ,  $f$  is zero  $Alk^6$  is in particular a  $C_{1-4}$  alkyl group as defined herein. When  $f$  is the integer 1, 2 or 3  $Alk^6$  is in particular a  $C_{1-3}$  alkylene chain.

Particular examples of aryl, heteroaryl, heterocycloaliphatic or cycloaliphatic groups which may be present in the group  $-R^{12a}$  or  $-R^{13a}$  include optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, azetidiny, pyrrolidinyl, pyrrolidinonyl, piperidinyl, imidazolidinyl, thiazolidinyl, piperazinyl,  $N-C_{1-6}$  alkylpiperazinyl, especially  $N$ -methylpiperazinyl,  $N-C_{1-6}$  alkylpyrrolidinyl, especially  $N$ -methylpyrrolidinyl,  $N-C_{1-6}$  alkylpiperidinyl, especially  $N$ -methylpiperidinyl, homopiperazinyl, morpholinyl, thiomorpholinyl, oxazolidinyl, tetrahydrofuranyl, tetrahydropyranyl, phenyl, pyrrolyl, furyl, thienyl, imidazolyl,  $N-C_{1-6}$  alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, tetrazolyl, triazinyl, pyridyl- $N$ -oxide, dihydropyrazolonyl or imidazolonyl.

Optional substituents which may in particular be present on the aryl, heteroaryl, heterocycloaliphatic or cycloaliphatic groups represented by  $-R^{12a}$  or  $-R^{13a}$  include one, two, three or more atoms or groups selected from fluorine, chlorine,  $C_{1-3}$  alkoxy, especially  $-OCH_3$ ,  $OCF_3$ ,  $OCF_2H$ ,  $CF_3$ ,  $C_{1-3}$  alkylthio, straight or branched  $C_{1-3}$  alkyl,  $-CN$ ,  $NHCH_3$ ,  $N(CH_3)_2$ ,  $CONH_2$ ,  $CONHCH_3$ ,  $CON(CH_3)_2$ ,  $CO_2CH_3$ ,  $CO_2CH_2CH_3$ ,  $-CO_2C(CH_3)_3$ , or  $-COCH_3$ ,  $-SO_2CH_3$ ,  $-NHCOCH_3$ ,  $-N(CH_3)COCH_3$  or  $CO_2H$ .

Where desired, two adjacent  $R^{12}$  substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a  $C_{1-6}$  alkylenedioxy group such as methylenedioxy or ethylenedioxy or a  $C_{3-6}$  cycloalkyl or 3-10 membered monocyclic heterocycloaliphatic group as defined herein.

It will be appreciated that where two or more  $R^{12}$  substituents are present, these need not necessarily be the same atoms and/or groups. In general, the substituent(s) may be present at any available ring position in the aromatic or heteroaromatic group.

The presence of certain substituents in the compounds of formula (1) may enable salts of the compounds to be formed. Suitable salts include pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, and salts derived from inorganic and organic bases.

Acid addition salts include hydrochlorides, hydrobromides, hydroiodides, alkylsulfonates, e.g. methanesulfonates, ethanesulfonates, or isothionates, arylsulfonates, e.g. *p*-toluenesulfonates, besylates or napsylates, phosphates, sulphates, hydrogen sulphates, acetates, trifluoroacetates, propionates, citrates, maleates, fumarates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

Salts derived from inorganic or organic bases include alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

Particularly useful salts of compounds according to the invention include pharmaceutically acceptable salts, especially acid addition pharmaceutically acceptable salts.

In one particular group of compounds of formula (1) X is an O atom.

Examples of cycloaliphatic groups which may represent R<sup>1</sup> include C<sub>3-6</sub> cycloalkyl groups, such as those described previously. Examples of cycloalkyl-alkyl- groups which may represent R<sup>1</sup> include C<sub>1-3</sub> alkyl groups (as described herein) where a terminal hydrogen atom is replaced by a C<sub>3-6</sub> cycloalkyl ring (as described herein), for example, cyclopropylCH<sub>2</sub>-.

R<sup>1</sup>, in compounds of formula (1), is in particular a C<sub>1-6</sub> alkyl group. Especially preferred is when R<sup>1</sup> is a C<sub>1-3</sub> alkyl group. Most especially preferred is when R<sup>1</sup> is a methyl group.

In another group of compounds of formula (1)  $R^1$  is a haloalkyl group, especially a  $CHF_2$  or  $CH_2F$  group.

A particularly preferred group of compounds of the invention has the formula  
 5 (1) wherein  $R^2$  is an optionally substituted monocyclic heteroaromatic group, especially a five-membered heteroaromatic group containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Particular preferred heteroaromatic groups which may represent  $R^2$  include  
 10 optionally substituted pyrrolyl, furyl, thienyl, imidazolyl, *N*- $C_{1-6}$ alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl or pyrazolyl. Especially preferred is when  $R^2$  is an oxazolyl group. Most especially preferred is where  $R^2$  is an oxazol-5-yl group.

Particular examples of the group  $R^3$ , in compounds of formula (1), include –  
 15  $Alk^1-L^1-Alk^2-R^4$ ,  $-Alk^1-L^1-R^4$ ,  $-Alk^1-R^4$ ,  $-L^1-Alk^2-R^4$ ,  $-L^1-R^4$  or  $-R^4$  wherein  $Alk^1$ ,  $L^1$ ,  $Alk^2$  and  $R^4$  are as herein defined. One particular group of compounds of the invention has the formula (1) wherein  $R^3$  is the group  $-Alk^1-L^1-R^4$ .

20  $Alk^1$  and  $Alk^2$ , when present in compounds of formula (1), may be the same or different and is each preferably an optionally substituted aliphatic chain, in particular a  $C_{1-6}$  alkylene chain, especially an optionally substituted  $-CH_2-$ ,  $-CH_2CH_2-$ ,  $-CH_2CH_2CH_2-$ ,  $-CH(CH_3)CH_2-$  or  $-CH_2CH(CH_3)-$  chain, most especially a  $C_{1-3}$  alkylene chain such as  $-CH_2-$ ,  $-CH_2CH_2-$  or  $-CH_2CH_2CH_2-$   
 25 chain.

Particular examples of  $L^1$ , when present in compounds of formula (1), include  $-O-$  or  $-S-$  atoms or  $-C(O)-$ ,  $-C(S)-$ ,  $-S(O)-$ ,  $-S(O)_2-$ ,  $-C(O)O-$ ,  $-OC(O)-$ ,  $-N(R^7)-$   
 [where  $R^7$  is as defined hereinbefore],  $-CON(R^7)-$ ,  $-CSN(R^7)-$ ,  $-N(R^7)CO-$ ,  
 30  $N(R^7)CS-$ ,  $-S(O)_2N(R^7)-$  or  $-N(R^7)S(O)_2-$  groups.  $R^7$  is especially a hydrogen atom or a  $C_{1-3}$  alkyl group, particularly methyl.

$L^1$  in one particular group of compounds of the invention is a covalent bond.

One particular class of compounds of the invention has the formula (1) wherein  $R^3$  is the chain  $-Alk^1-L^1-R^4$  in which  $Alk^1$  is an optionally substituted aliphatic chain,  $L^1$  is a covalent bond and  $R^4$  is a hydrogen atom. In one particular group of compounds of this class  $R^3$  is especially a straight or branched  $C_{1-6}$  alkyl group, particularly  $-CH_3$ ,  $-CH_2CH_3$ ,  $-CH(CH_3)_2$ ,  $-(CH_2)_2CH_3$  or  $-C(CH_3)_3$ . In this group of compounds  $R^3$  is preferably a methyl or ethyl group, most especially a methyl group.

Another class of compounds of the invention has the formula (1) wherein  $R^3$  is a hydrogen atom.

In one particular embodiment of the invention  $R^3$  is a hydrogen atom or a  $C_{1-6}$  alkyl group, particularly methyl.

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In one group of compounds of the invention A is an optionally substituted, optionally fused  $C_{3-6}$  cycloaliphatic group or 3 to 6 membered saturated monocyclic hydrocarbon ring system containing one or two  $L^4$  linker atoms or groups. Particular examples of suitable  $L^4$  atoms or groups include  $-O-$  or  $-S-$  atoms or  $-C(O)-$ ,  $-C(S)-$ ,  $-S(O)_2-$ ,  $-N(R^7)-$  [where  $R^7$  is as defined above],  $-CON(R^7)-$ ,  $-CSN(R^7)-$ ,  $-N(R^7)CO-$ ,  $-N(R^7)CS-$ ,  $-S(O)_2N(R^7)$ ,  $-N(R^7)S(O)_2-$ , groups. Particular examples of the group A include optionally substituted cyclopentyl, cyclopentenyl, cyclohexyl, cyclopentanonyl, cyclohexanonyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolinyl, e.g. 2- or 3-pyrrolinyl, pyrrolidinyl, pyrrolidinonyl, piperidinyl, piperidinonyl,  $N-C_{1-6}$  alkylpyrrolidinyl,  $N-C_{1-6}$  alkylpiperidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, tetrahydrothiopyranyl 1,1-dioxide or tetrahydrothiophenyl 1,1-dioxide.

More particular examples of the group A include optionally substituted cyclopentyl, cyclohexyl, cyclopentanonyl, cyclohexanonyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, pyrrolidinonyl, piperidinyl, piperidinonyl,  $N-C_{1-6}$  alkylpyrrolidinyl or  $N-C_{1-6}$  alkylpiperidinyl. A is in particular an optionally substituted cyclopentyl, cyclohexyl, tetrahydrofuranyl, tetrahydropyranyl,

pyrrolidinyl, piperidinyl, *N*-C<sub>1-6</sub> alkylpyrrolidinyl, especially *N*-methylpyrrolidinyl, or *N*-C<sub>1-6</sub> alkylpiperidinyl, especially *N*-methylpiperidinyl group.

In another particular group of compounds of formula (1) A is an optionally substituted cyclopentyl, cyclohexyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, pyrrolidinonyl, piperidinyl, tetrahydrothiophenyl or tetrahydrothiophenyl 1,1-dioxide group. Typical examples of A include optionally substituted cyclopentyl, cyclohexyl, tetrahydrofuran-3-yl, tetrahydropyran-4-yl, pyrrolidin-3-yl, pyrrolidin-2-on-3-yl, piperidin-4-yl, tetrahydrothiophen-3-yl or tetrahydrothiophen-3-yl 1,1-dioxide group.

One particular class of compounds of the invention has the formula (1) wherein A is an optionally substituted cycloaliphatic or heterocycloaliphatic group fused to an optionally substituted aryl or heteroaryl group.

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Particular examples of aryl or heteroaryl groups which may be fused to the group A include optionally substituted monocyclic C<sub>6-12</sub>aromatic groups, such as phenyl or optionally substituted monocyclic C<sub>1-9</sub>heteroaromatic groups, especially 5 or 6 membered heteroaromatic groups, containing for example one, two, three or four heteroatoms selected from oxygen, sulfur or nitrogen atoms as defined hereinbefore.

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One particular group of aryl or heteroaryl groups which may be fused to the group A include optionally substituted phenyl, pyrrolyl, furyl, thienyl, imidazolyl, *N*-C<sub>1-6</sub>alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl or pyridyl-*N*-oxide. More particular examples include optionally substituted imidazolyl, *N*-C<sub>1-6</sub>alkylimidazolyl, phenyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl or pyridyl-*N*-oxide.

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In one particular class of compounds of the invention A is an optionally substituted cyclopentyl, tetrahydrofuranyl, pyrrolidinyl, *N*-C<sub>1-6</sub> alkylpyrrolidinyl, especially *N*-methylpyrrolidinyl, group fused to an optionally substituted imidazolyl, *N*-C<sub>1-6</sub>alkylimidazolyl, phenyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl or pyridyl-*N*-oxide group. In one group of compounds of the

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invention A forms an optionally substituted indanyl group. A may also in particular be an optionally substituted 5,6-dihydro-4H-cyclopenta[b]thiophenyl or tetrahydronaphthyl group. Typical examples of A include indan-1-yl, indan-2-yl, 5-nitroindan-2-yl, 5-aminoindan-2-yl, 5-*tert*-butoxycarbonylaminoindan-2-yl, 5,6-dihydro-4H-cyclopenta[b] thiophen-5-yl or 1,2,3,4-tetrahydronaphth-2-yl groups.

Particular examples of the group  $R^5$ , in compounds of formula (1), include  $-Alk^3-L^2-Alk^4-R^6$ ,  $-Alk^3-L^2-R^6$ ,  $-Alk^3-R^6$ ,  $-L^2-Alk^4-R^6$ ,  $-L^2-R^6$  or  $-R^6$  wherein  
10  $Alk^3$ ,  $L^2$ ,  $Alk^4$  and  $R^6$  are as herein defined.

In one particular embodiment of the invention  $t$  is zero. In another particular embodiment of the invention  $t$  is the integer 1.

15  $v$  in one particular aspect of the invention is zero. In another embodiment  $v$  is the integer 1.

$Alk^3$  and  $Alk^4$ , when present in compounds of formula (1), may be the same or different and is each preferably an optionally substituted aliphatic chain, in particular a  $C_{1-6}$  alkylene chain, most especially a  $C_{1-3}$  alkylene chain.

$Alk^3$  in one particular group of compounds of the invention is a  $-CH_2-$  chain.

Particular examples of  $Alk^4$  in compounds of the invention include  $-CH_2-$ ,  
25  $-CH_2CH_2-$ ,  $-CH(CH_3)CH_2-$ ,  $-C(CH_3)_2-$ ,  $-CH_2C(CH_3)_2CH_2-$  or  $-(CH_2)_2C(CH_3)_2CH_2-$  chains.

Optional substituents which may in particular be present on  $Alk^3$  and/ or  $Alk^4$  include  $-CN$ ,  $-CO_2H$ ,  $-CO_2R^{11}$  [where  $R^{11}$  is as herein defined]  $-CONHR^{11}$ ,  
30  $-CON(R^{11})_2$ ,  $-COR^{11}$ ,  $C_{1-6}$ alkoxy, particularly methoxy or ethoxy; halo $C_{1-6}$ alkoxy, particularly trifluoromethoxy or difluoromethoxy;  $-S(O)R^{11}$ ,  $-S(O)_2R^{11}$ , amino,  $-NHR^{11}$  or  $-N(R^{11})_2$ , groups.  $R^{11}$  is in particular a  $C_{1-3}$  alkyl group.

Particular examples of  $L^2$ , when present in compounds of formula (1), include  
 -O- or -S- atoms or -C(O)-, -C(S)-, -S(O)-, -S(O)<sub>2</sub>-, -C(O)O-, -OC(O)-, -N(R<sup>7</sup>)-  
 [where R<sup>7</sup> is as defined hereinbefore], -CON(R<sup>7</sup>)-, -CSN(R<sup>7</sup>)-, -N(R<sup>7</sup>)CO-,  
 -N(R<sup>7</sup>)CS-, -S(O)<sub>2</sub>N(R<sup>7</sup>)- or -N(R<sup>7</sup>)S(O)<sub>2</sub>- groups.  $L^2$  may also, in particular, be  
 5 a -N(R<sup>7</sup>)C(O)O-, -C(O)N(R<sup>7</sup>)C(O)- or -C(O)N(R<sup>7</sup>)O- group. R<sup>7</sup> is especially a  
 hydrogen atom or a C<sub>1-3</sub> alkyl group, particularly methyl. Typical examples of  
 $L^2$  include -C(O)-, -S(O)<sub>2</sub>-, -C(O)O-, -CON(H)-, -CON(CH<sub>3</sub>)-, -CON(CH<sub>2</sub>CH<sub>3</sub>)-,  
 -CON(CH(CH<sub>3</sub>)<sub>2</sub>)-, -N(H)CO-, -N(H)C(O)O-, -C(O)N(H)C(O)- or  
 -C(O)N(CH<sub>3</sub>)O-.

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$L^2$  in one particular group of compounds of the invention is a covalent bond.

R<sup>6</sup> in compounds of formula (1) is in particular a hydrogen or halogen atom or  
 an optionally substituted C<sub>3-6</sub> cycloalkyl, 5 to 7 membered heterocycloalkyl,  
 15 phenyl or a 5 to 10 membered heteroaryl group.

Particular R<sup>6</sup> examples include hydrogen or fluorine or optionally substituted  
 cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, azetidiny, pyrrolidinyl,  
 pyrrolidinonyl, piperidinyl, imidazolidinyl, thiazolidinyl, piperazinyl, N-C<sub>1-6</sub>  
 20 alkylpiperazinyl, especially N-methylpiperazinyl, N-C<sub>1-6</sub> alkylpyrrolidinyl,  
 especially N-methylpyrrolidinyl, N-C<sub>1-6</sub> alkylpiperidinyl, especially N-  
 methylpiperidinyl, homopiperazinyl, morpholinyl, thiomorpholinyl, oxazolidinyl,  
 tetrahydrofuranyl, tetrahydropyranyl, phenyl, pyrrolyl, furyl, thienyl, imidazolyl,  
 N-C<sub>1-6</sub>alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl,  
 25 triazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl,  
 tetrazolyl, triazinyl, pyridyl-N-oxide, benzofuryl, benzothienyl or indolyl. More  
 particular examples include optionally substituted cyclopropyl, cyclopentyl,  
 cyclohexyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydropyranyl,  
 phenyl, pyrrolyl, furyl, thienyl, imidazolyl, isoxazolyl, pyridyl, pyrimidinyl,  
 30 benzofuryl or benzothienyl.

Typical values of R<sup>6</sup> include hydrogen, cyclopropyl, cyclopentyl, cyclohexyl,  
 pyrrolidin-1-yl, piperidin-1-yl, piperidin-4-yl, 1-(*tert*-butoxycarbonyl)piperidin-4-

yl, 1-acetylpiperidin-4-yl, 4-(4-chlorophenoxy)piperidin-1-yl, 4-trifluoromethylpiperidin-1-yl, 4-(2-fluorophenyl)piperidin-1-yl, 4-(pyridyl-4-oxy)piperidin-1-yl, 4-(benzofur-2-yl)piperidin-1-yl, 4-methylpiperazin-1-yl, 4-(*tert*-butoxycarbonyl)piperazin-1-yl, morpholin-1-yl, tetrahydropyran-4-yl, phenyl, 3-aminophenyl, 3-aminomethylphenyl, 3-[(*tert*-butoxycarbonyl)aminomethyl]phenyl, 3-[(tetrahydrofur-3yloxycarbonyl)aminomethyl]phenyl, 2-fluorophenyl, 2,4-difluorophenyl, 2-chlorophenyl, 2-trifluoromethoxyphenyl, 2-trifluoromethylphenyl, 4-methoxycarbonylphenyl, 4-carboxyphenyl, 4-methoxyphenyl, pyrrol-2-yl, 1-methylpyrrol-2-yl, fur-2-yl, 5-[4-(trifluoromethyl)phenyl]fur-2-yl, fur-3-yl, thien-3-yl, 1-methylimidazol-2-yl, 3,5-dimethylisoxazol-4-yl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, pyrimidin-2-yl or benzothien-3-yl.

One class of compounds of the invention has the formula (1) wherein  $R^5$  is the chain  $-Alk^3-L^2-R^6$  in which  $Alk^3$  is an optionally substituted aliphatic chain,  $L^2$  is a covalent bond and  $R^6$  is a hydrogen atom.  $Alk^3$  in compounds of this type is preferably a straight or branched  $C_{1-6}$  alkylene chain as herein defined, especially  $-CH_2-$ ,  $-CH_2CH_2-$ ,  $-(CH_2)_2CH_2-$ ,  $-(CH_2)_3CH_2-$  or  $-CH_2C(CH_3)_2-$ . Optional substituents present on these chains include those as herein defined for  $Alk^3$  substituents, especially  $-CN$ ,  $-CO_2H$ ,  $-CO_2R^{11}$  [where  $R^{11}$  is as herein defined]  $-CONHR^{11}$ ,  $-CON(R^{11})_2$ ,  $-COR^{11}$ ,  $C_{1-6}$  alkoxy, particularly methoxy or ethoxy; halo $C_{1-6}$ alkoxy, particularly trifluoromethoxy or difluoromethoxy;  $-S(O)R^{11}$ ,  $-S(O)_2R^{11}$ , amino,  $-NHR^{11}$  or  $-N(R^{11})_2$  groups.  $R^{11}$  is in particular a  $C_{1-3}$  alkyl group. In one particular group of compounds of this type  $Alk^1$  is a  $-CH_2-$ ,  $-CH_2CH_2-$ ,  $-CH_2CH_2CH_2-$  or  $-CH_2CH_2CH_2CH_2-$  chain substituted with a  $-NH(CH_3)$ ,  $-N(CH_3)_2$ ,  $-CN$ ,  $-CO_2H$ ,  $-CO_2CH_3$ ,  $-CO_2CH_2CH_3$ ,  $-CO_2C(CH_3)_3$ ,  $-CONH_2$ ,  $-CONHCH_3$  or  $-CON(CH_3)_2$  group. Typical examples of  $R^5$  in compounds of this type include methyl,  $-(CH_2)_2C(CH_3)_3$ ,  $-CH_2CO^tBu$  or  $-CH_2CON(CH_3)_2$ .

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Another class of compounds of the invention has the formula (1) wherein  $R^5$  is the chain  $-Alk^3-L^2-R^6$  in which  $Alk^3$  is an optionally substituted aliphatic chain,  $L^2$  is a covalent bond or a linker atom or group and  $R^6$  is an optionally



substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group especially an optionally substituted heterocycloaliphatic, aromatic or heteroaromatic group.  $\text{Alk}^3$  in compounds of this type is in particular an optionally substituted  $\text{C}_{1-6}$  alkylene chain, especially  $-\text{CH}_2-$ ,  $\text{CH}_2\text{CH}_2-$  or  $-\text{CH}_2\text{CH}_2\text{CH}_2-$ .  $\text{R}^6$  in compounds of this type is especially an optionally substituted 3-10 membered saturated monocyclic heterocycloaliphatic, phenyl or monocyclic heteroaromatic group. Particular  $\text{R}^6$  examples include optionally substituted azetidiny, pyrrolidiny, pyrrolidinonyl, piperidiny, imidazolidiny, thiazolidiny, piperaziny,  $N\text{-C}_{1-6}$  alkylpiperaziny, especially  $N$ -methylpiperaziny,  $N\text{-C}_{1-6}$  alkylpyrrolidiny, especially  $N$ -methylpyrrolidiny,  $N\text{-C}_{1-6}$  alkylpiperidiny, especially  $N$ -methylpiperidiny, homopiperaziny, morpholiny, thiomorpholiny, oxazolidiny, tetrahydrofurany, tetrahydropyrany, phenyl, pyrroly, furyl, thienyl, imidazolyl,  $N\text{-C}_{1-6}$  alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyrimidiny, pyridaziny, pyraziny, tetrazolyl, triaziny, pyridyl- $N$ -oxide, dihydropyrazolonyl or imidazolonyl. A typical example of  $\text{R}^5$  in compounds of this type includes  $-\text{CH}_2\text{phenyl}$ .

In another class of compounds of the invention  $\text{R}^5$  is the chain  $-\text{L}^2\text{-(Alk}^4\text{)}_v\text{-R}^6$  in which  $\text{L}^2$  is a linker atom or group,  $\text{Alk}^4$  is an optionally substituted aliphatic or heteroaliphatic chain,  $v$  is zero or the integer 1 and  $\text{R}^6$  is a hydrogen atom or an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group, as defined herein.

$\text{Alk}^4$  in compounds of this class is preferably an optionally substituted straight or branched  $\text{C}_{1-6}$  alkylene chain as defined herein or a  $-\text{CH}_2\text{L}^3-$  [where  $\text{L}^3$  is as defined herein],  $-\text{CH}(\text{CH}_3)\text{L}^3-$ ,  $-\text{CH}_2\text{L}^3\text{CH}_2-$ ,  $-\text{CH}(\text{CH}_3)\text{CH}_2\text{L}^3-$ ,  $-\text{CH}_2\text{CH}_2\text{L}^3-$ ,  $-\text{CH}_2\text{L}^3\text{CH}_2\text{CH}_2-$ ,  $-(\text{CH}_2)_2\text{L}^3\text{CH}_2-$ ,  $-(\text{CH}_2)_3\text{L}^3\text{CH}_2-$  or  $-(\text{CH}_2)_3\text{L}^3-$  chain, most especially a  $\text{C}_{1-6}$  alkylene chain.  $\text{R}^6$  is preferably a hydrogen atom or an optionally substituted  $\text{C}_{3-6}$  cycloalkyl, 3-10 membered saturated monocyclic heterocycloaliphatic, phenyl or monocyclic heteroaromatic group. In one group of compounds of this class  $\text{L}^2$  is in particular  $-\text{O}-$ ,  $-\text{N}(\text{R}^7)-$ ,  $-\text{C}(\text{O})-$ ,  $-\text{C}(\text{S})-$ ,  $-\text{S}(\text{O})_2-$ ,  $-\text{C}(\text{O})\text{O}-$ ,  $-\text{OC}(\text{O})-$ ,  $-\text{CON}(\text{R}^7)-$ ,  $-\text{CSN}(\text{R}^7)-$ ,  $-\text{N}(\text{R}^7)\text{CO}-$  or  $-\text{N}(\text{R}^7)\text{CS}-$ ,

[where  $R^7$  is especially a hydrogen atom or a methyl group] and  $Alk^4$  is most preferably an optionally substituted  $C_{1-3}$  alkylene chain, especially  $-CH_2-$ ,  $CH_2CH_2-$  or  $-CH_2CH_2CH_2-$ . In another particular group of compounds of this class  $L^2$  is a  $-C(O)-$ ,  $-C(O)O-$ ,  $-S(O)_2-$ ,  $-CON(R^7)$ ,  $-N(R^7)C(O)O-$  or

5  $-C(O)N(R^7)CO-$  group. Optional substituents which may in particular be present on  $Alk^4$  include  $-CN$ ,  $-CO_2H$ ,  $-CO_2R^{11}$  [where  $R^{11}$  is as herein defined]  $-CONHR^{11}$ ,  $-CON(R^{11})_2$ ,  $-COR^{11}$ ,  $C_{1-6}$ alkoxy, particularly methoxy or ethoxy; halo $C_{1-6}$ alkoxy, particularly trifluoromethoxy or difluoromethoxy;  $-S(O)R^{11}$ ,  $-S(O)_2R^{11}$ , amino,  $-NHR^{11}$  or  $-N(R^{11})_2$ , groups.  $R^{11}$  is in particular a  $C_{1-3}$  alkyl

10 group.

Another class of compounds has the formula (1) wherein  $R^5$  is the group  $R^6$ . In compounds of this class  $R^6$  is in particular a halogen atom a  $-CN$  group or an optionally substituted  $C_{3-6}$  cycloalkyl, 3-10 membered saturated monocyclic

15 heterocycloaliphatic, phenyl or monocyclic heteroaromatic group. A typical example of  $R^6$  in compounds of this type includes pyrid-2-yl.

In another class of compounds of the invention  $R^5$  is the chain  $-Alk^3-L^2-Alk^4-R^6$  in which  $Alk^3$  is an optionally substituted aliphatic chain,  $L^2$  is a linker atom or group,  $Alk^4$  is an optionally substituted aliphatic or heteroaliphatic chain and

20  $R^6$  is a hydrogen atom or an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group.

One particular group of compounds according to the invention has the formula

25 (1) wherein  $R^5$  is a  $C_{1-6}$  alkyl group, especially a  $C_{1-3}$  alkyl group, most especially a methyl group.

Another particular group of compounds of the invention has the formula (1) wherein  $R^5$  is a hydrogen atom.

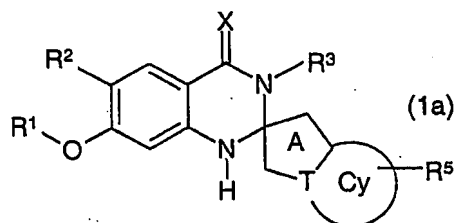
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One group of cycloaliphatic or heterocycloaliphatic substituents, which may be present on the groups A,  $R^4$  or  $R^6$ , are one, two, three or more groups selected from  $C_{1-3}$  alkoxy,  $OCF_3$ ,  $OCF_2H$ ,  $CF_3$ ,  $C_{1-3}$  alkylthio, optionally substituted straight or branched  $C_{1-3}$  alkyl (wherein the optional alkyl substituent is in

particular an optionally substituted phenyl or monocyclic heteroaromatic group), optionally substituted phenyl or monocyclic heteroaromatic group, -CN, NHCH<sub>3</sub>, N(CH<sub>3</sub>)<sub>2</sub>, CONH<sub>2</sub>, CONHCH<sub>3</sub>, CON(CH<sub>3</sub>)<sub>2</sub>, CO<sub>2</sub>CH<sub>3</sub>, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -CO<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>, or -COCH<sub>3</sub>, -NHCOCH<sub>3</sub>, -N(CH<sub>3</sub>)COCH<sub>3</sub> or  
 5 CO<sub>2</sub>H. Further substituents, which may in particular be present on R<sup>6</sup>, include *tert*-butoxycarbonyl, optionally substituted phenoxy e.g. 4-chlorophenoxy, pyridyloxy e.g. pyrid-4-yloxy.

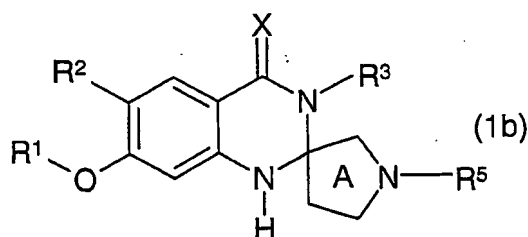
One group of aromatic or heteroaromatic substituents, which may be present  
 10 on the groups R<sup>4</sup> or R<sup>6</sup>, or the aryl or heteroaryl group optionally fused to the group A, are one, two, three or more atoms or groups selected from fluorine, chlorine, straight or branched C<sub>1-6</sub> alkyl, optionally substituted morpholinyl, thiomorpholinyl, piperazinyl, pyrrolidinyl, piperidinyl, methoxy, OCF<sub>3</sub>, OCF<sub>2</sub>H, CF<sub>3</sub>, CN, NHCH<sub>3</sub>, N(CH<sub>3</sub>)<sub>2</sub>, CONH<sub>2</sub>, CONHCH<sub>3</sub>, CON(CH<sub>3</sub>)<sub>2</sub>, CO<sub>2</sub>CH<sub>3</sub>,  
 15 CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -CO<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>, or -COCH<sub>3</sub>, -NHCOCH<sub>3</sub>, -N(CH<sub>3</sub>)COCH<sub>3</sub>, -SCH<sub>3</sub>, -SO<sub>2</sub>CH<sub>3</sub> or CO<sub>2</sub>H.

One particular class of compounds of the invention has the formula (1a):



20 in which A is an optionally substituted cyclopentyl ring fused to a group Cy in which Cy is an optionally substituted phenyl or monocyclic C<sub>1-9</sub> heteroaromatic group, especially a 5 or 6 membered heteroaromatic group, containing for example one, two, three or four heteroatoms selected from oxygen, sulfur or nitrogen atoms as defined hereinbefore; T is a carbon or nitrogen atom; R<sup>1</sup>,  
 25 R<sup>2</sup>, R<sup>3</sup>, R<sup>5</sup> and X are as defined and further defined for compounds of formula (1).

Another particular class of compounds of the invention has the formula (1b):



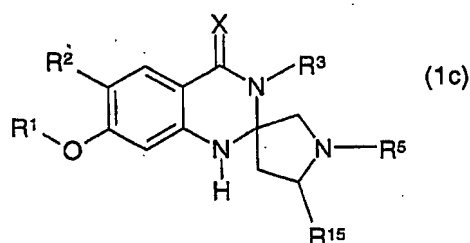
in which A is an optionally substituted pyrrolidinyl ring;  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^5$  and X are as defined and further defined for compounds of formula (1).

- 5 In one particular class of compounds of formula (1b)  $R^5$  is a group  $-L^2-(Alk^4)_v-R^6$  in which  $L^2$  is a linker atom or group,  $Alk^4$  is an optionally substituted aliphatic or heteroaliphatic chain,  $v$  is zero or the integer 1 and  $R^6$  is a hydrogen atom or an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group, as defined herein.
- 10  $Alk^4$  in compounds of this type is preferably an optionally substituted straight or branched  $C_{1-6}$  alkylene chain as defined herein or a  $-CH_2L^3-$  [where  $L^3$  is as defined herein],  $-CH(CH_3)L^3-$ ,  $-CH_2L^3CH_2-$ ,  $-CH(CH_3)CH_2L^3-$ ,  $-CH_2CH_2L^3-$ ,  $-CH_2L^3CH_2CH_2-$ ,  $-(CH_2)_2L^3CH_2-$ ,  $-(CH_2)_3L^3CH_2-$  or  $-(CH_2)_3L^3-$  chain, most especially a  $C_{1-6}$  alkylene chain.  $R^6$  is preferably a hydrogen atom or an
- 15 optionally substituted  $C_{3-6}$  cycloalkyl, 3-10 membered saturated monocyclic heterocycloaliphatic, phenyl or monocyclic heteroaromatic group. In one group of compounds of this class  $L^2$  is in particular  $-C(O)-$ ,  $-C(S)-$ ,  $-S(O)_2-$ ,  $-C(O)O-$ ,  $-CON(R^7)-$  or  $-CSN(R^7)-$  [where  $R^7$  is especially a hydrogen atom or a methyl group] and  $Alk^4$  is most preferably an optionally substituted  $C_{1-3}$
- 20 alkylene chain, especially  $-CH_2-$ ,  $CH_2CH_2-$  or  $-CH_2CH_2CH_2-$ . In another particular group of compounds of this class  $L^2$  is a  $-C(O)-$ ,  $-C(O)O-$ ,  $-S(O)_2-$ ,  $-CON(R^7)$ ,  $-N(R^7)C(O)O-$  or  $-C(O)N(R^7)CO-$  group. Optional substituents which may in particular be present on  $Alk^4$  include  $-CN$ ,  $-CO_2H$ ,  $-CO_2R^{11}$  [where  $R^{11}$  is as herein defined]  $-CONHR^{11}$ ,  $-CON(R^{11})_2$ ,  $-COR^{11}$ ,  $C_{1-6}$ alkoxy, particularly methoxy or ethoxy; halo $C_{1-6}$ alkoxy, particularly trifluoromethoxy or difluoromethoxy;  $-S(O)R^{11}$ ,  $-S(O)_2R^{11}$ , amino,  $-NHR^{11}$  or  $-N(R^{11})_2$  groups.  $R^{11}$  is in particular a  $C_{1-3}$  alkyl group.

One particular group of compounds of this type has the formula (1b) wherein

30  $L^2$  is a linker group selected from  $-C(O)-$ ,  $-C(S)-$ ,  $-S(O)_2-$ , especially  $-C(O)-$ ,  $v$

- is zero and  $R^6$  is an optionally substituted 3-10 membered saturated monocyclic heterocycloaliphatic group which contains one or more N atoms or groups, wherein the heterocycloaliphatic group is attached to the group  $L^2$  through any available N atom. Particular examples of  $R^6$  groups of this type
- 5 include optionally substituted azetidiny, pyrrolidinyl, piperidinyl, imidazolidinyl, thiazolidinyl, pyrazolidinyl, piperazinyl,  $N$ - $C_{1-6}$  alkylpiperazinyl, homopiperazinyl, morpholinyl, thiomorpholinyl or oxazolidinyl, especially optionally substituted pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl.
- 10 A further particular class of compounds of the invention has the formula (1c):



- wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^5$  and  $X$  are defined for compounds of formulae (1) and (1b);  $R^{15}$  is a group selected from  $-CN$ ,  $-CO_2R^{10a}$  [where  $R^{10a}$  is a hydrogen atom or a  $C_{1-6}$ alkyl group],  $-AlkOR^{10a}$  [where  $Alk$  is a  $C_{1-3}$ alkylene chain],  $-NR^{10a}COR^{16}$  [where  $R^{16}$  is a  $C_{1-6}$ alkyl group],  $-NR^{10a}SO_2R^{16}$ ,  $-SO_2R^{16}$ ,  $-COR^{16}$ ,  $-CONR^{17}R^{18}$  [where  $R^{17}$  and  $R^{18}$ , which may be the same or different, is each a hydrogen atom or a  $C_{1-6}$ alkyl group, or  $R^{17}$  and  $R^{18}$  may join together to form a 4 to 6 membered heterocycloalkyl group],  $-NR^{17}R^{18}$ ,  $-SO_2NR^{17}R^{18}$ ,  $C_{1-6}$ alkyl, halo $C_{1-6}$ alkyl or 5 or 6 membered heteroaryl group.

- 20  $R^{15}$  in one particular group of compounds of formula (1c) is selected from  $-CN$ ,  $-CO_2R^{10a}$ ,  $-AlkOR^{10a}$ ,  $-NR^{10a}COR^{16}$ ,  $-CONR^{17}R^{18}$ ,  $-NR^{17}R^{18}$ , or optionally substituted  $C_{1-6}$ alkyl or 5 or 6 membered heteroaryl group.

- 25 In one particularly preferred group of compounds of formula (1c)  $R^{15}$  is selected from  $-CN$ ,  $-CO_2R^{10a}$ ,  $-AlkOR^{10a}$ ,  $-CONR^{17}R^{18}$ , or a 5 or 6 membered heteroaryl group. One particularly preferred group of compounds has the formula (1c) wherein  $R^{15}$  is a  $-CO_2R^{10a}$  or  $-CONR^{17}R^{18}$  group.

Particular C<sub>1-6</sub> alkyl groups, which may represent the groups R<sup>10a</sup>, R<sup>16</sup>, R<sup>17</sup> or R<sup>18</sup> in compounds of formula (1c), include methyl, ethyl, propyl or isopropyl.

Alk in compounds of formula (1c) is preferably a C<sub>1-3</sub> alkylene chain, especially methylene or ethylene.

Particular heterocycloalkyl groups, which may represent NR<sup>17</sup>R<sup>18</sup>, include 4 – 6 membered heterocycloalkyl groups selected from azetidiny, pyrrolidiny, piperidiny, imidazolidiny, thiazolidiny, pyrazolidiny, piperaziny, N-C<sub>1-6</sub> alkylpiperaziny, morpholiny, thiomorpholiny, oxazolidiny, most particularly pyrrolidiny.

Particular heteroaryl groups which may represent R<sup>15</sup> include optionally substituted 5 membered groups selected from pyrrolyl, furyl, thienyl, imidazolyl, N-C<sub>1-6</sub>alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, oxadiazolyl, thiadiazolyl or tetrazolyl, especially 3-methyl oxadiazolyl.

Typical examples of the group R<sup>15</sup> include –CO<sub>2</sub>CH<sub>3</sub>, –CO<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, –CO<sub>2</sub>H, CON(CH<sub>3</sub>)<sub>2</sub>, –C(O)pyrrolidin-1-yl or 3-methyloxadiazolyl.

Typical examples of R<sup>5</sup> in compounds of formula (1c) include H, –CO<sub>2</sub>CH<sub>3</sub>, –CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, –CO<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, –CO<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>, –C(O)fur-2-yl, –C(O)piperidin-1-yl, –CON(CH<sub>3</sub>)phenyl or –C(O)N(CH<sub>3</sub>)OCH<sub>3</sub>.

Compounds of formula (1) are potent inhibitors of IMPDH. The ability of the compounds to act in this way may be simply determined by employing tests such as those described in the Examples hereinafter.

Thus the compounds of the invention may be used in the treatment of IMPDH-associated disorders. The invention extends to such a use and in general to the use of the compounds of formula (1) for the manufacture of a medicament for treating such diseases and disorders.

"IMPDH-associated disorders" refers to any disorder or disease state in which inhibition of the enzyme IMPDH (inosine monophosphate dehydrogenase, EC1.1.1.205, of which there are presently two known isozymes referred to as IMPDH type 1 and IMPDH type 2) would modulate the activity of cells (such as lymphocytes or other cells) and thereby ameliorate or reduce the symptoms or modify the underlying cause(s) of that disorder or disease. There may or may not be present in the disorder or disease an abnormality associated directly with the IMPDH enzyme. Examples of IMPDH-associated disorders include transplant rejection and autoimmune disorders, such as rheumatoid arthritis, lupus, multiple sclerosis, juvenile diabetes, asthma, and inflammatory bowel disease, as well as inflammatory disorders, cancer and tumors, T-cell mediated hypersensitivity diseases, ischemic or reperfusion injury, viral replication diseases, proliferative disorders and vascular diseases.

Use of the compounds of the present invention is exemplified by, but is not limited to, treating a range of disorders such as: treatment of transplant rejection (e.g. kidney, liver, heart, lung, pancreas (e.g., islet cells), bone marrow, cornea, small bowel, skin allografts, skin homografts (such as employed in burn treatment), heart valve xenografts, serum sickness, and graft vs. host disease, in the treatment of autoimmune diseases, such as rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, juvenile diabetes, asthma, inflammatory bowel disease (such as Crohn's disease and ulcerative colitis), pyoderma gangrenum, lupus (systemic lupus erythematosus), myasthenia gravis, psoriasis, eczema, dermatitis, dermatomyositis, atopic dermatitis; multiple sclerosis, seborrhoea, pulmonary inflammation, eye uveitis, hepatitis, Grave's disease, Hashimoto's thyroiditis, autoimmune thyroiditis, Behcet's or Sjorgen's syndrome (dry eyes/mouth), pernicious or immunohaemolytic anaemia, Addison's disease (autoimmune disease of the adrenal glands), idiopathic adrenal insufficiency, autoimmune polyglandular disease (also known as autoimmune polyglandular syndrome) glomerulonephritis, scleroderma, morphea, lichen planus, viteligo (depigmentation of the skin), alopecia areata, autoimmune alopecia, autoimmune hypopituitarism, cicatricial pemphigoid, Gullivan-Barre syndrome, and alveolitis; in the treatment of T-cell mediated hypersensitivity

diseases, including contact hypersensitivity, delayed-type hypersensitivity, contact dermatitis (including that due to poison ivy), urticaria, skin allergies, respiratory allergies (hayfever, allergic rhinitis) and gluten-sensitive enteropathy (Celiac disease); in the treatment of inflammatory diseases such as osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma, acute respiratory distress syndrome, Sezary's syndrome and vascular diseases which have an inflammatory and or a proliferatory component such as restenosis, stenosis and arteriosclerosis; in the treatment of cancer and tumor disorders, such as solid tumors, lymphomas and leukemia; in the treatment of fungal infections such as mycosis fungoides; in protection from ischemic or reperfusion injury such as ischemic or reperfusion injury that may have been incurred during organ transplantation, myocardial infarction, stroke or other causes; in the treatment of DNA or RNA viral replication diseases, such as herpes simplex type 1 (HSV-1), herpes simplex type 2 (HSV-2), hepatitis (including hepatitis B and hepatitis C) cytomegalovirus, Epstein-Barr, human immunodeficiency virus (HIV) and influenza.

Additionally, IMPDH is also known to be present in bacteria and thus may regulate bacterial growth. As such, the IMPDH-inhibitor compounds of the present invention may be useful in treatment or prevention of bacterial infection, alone or in combination with other antibiotic agents.

In a particular embodiment, the compounds of the present invention are useful for the treatment of the afore mentioned exemplary disorders irrespective of their etiology, for example, for the treatment of lupus, psoriasis, inflammatory bowel disease, multiple sclerosis, atopic dermatitis, transplant rejection or rheumatoid arthritis.

In another particular embodiment the compounds of the present invention are of particular use for the treatment of DNA or RNA viral replication diseases, such as hepatitis (including hepatitis B and hepatitis C) cytomegalovirus, human immunodeficiency virus (HIV) and influenza.



In an additional particular embodiment the compounds of the present invention are of particular use for the treatment of cancer and tumour disorders, such as solid tumors, lymphoma, leukemia and other forms of cancer.

5

The compounds of formula (1) can be used alone or in combination with other therapeutic or prophylactic agents, such as anti-virals, anti-inflammatory agents, antibiotics, anticancer agents and immunosuppressants.

- 10 For the prophylaxis or treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formula (1) together with one or more pharmaceutically acceptable carriers, excipients or diluents.

15

Alternate compositions of this invention comprise a compound formula (1) or a salt thereof; an additional agent selected from an immunosuppressant, an anti-cancer agent, an anti-viral agent, anti-inflammatory agent, anti-fungal agent, anti-vascular hyperproliferation agent or an antibiotic agent; and any

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Thus, for example, additional immunosuppression agents include, but are not limited to, cyclosporin A, FK506, rapamycin, leflunomide, deoxyspergualin, prednisone, azathioprine, OKT3, ATAG, interferon and mizoribine. Additional

25 anti-cancer agents include, but are not limited to, cis-platin, actinomycin D, doxorubicin, vincristine, vinblastine, etoposide, amsacrine, mitoxantrone, tenipaside, taxol, colchicine, cyclosporin A, phenothiazines, interferon and thioxantheres. Additional anti-viral agents include, but are not limited to, Cytovene, Ganiclovir, trisodium phosphonoformate, Ribavirin, d4T, ddI, AZT

30 and acyclovir. Additional anti-vascular hyperproliferative agents include, but are not limited to, HMG Co-A reductase inhibitors such as lovastatin, thromboxane A2 synthetase inhibitors, eicosapentanoic acid, ciprostone, trapidil, ACE inhibitors, low molecular weight heparin, and rapamycin.

The above other therapeutic agents, when employed in combination with the compounds of the present invention, may be used, for example, in those amounts indicated in the Physician's Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art.

5

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical, vaginal or rectal administration, or a form suitable for administration by inhalation or insufflation.

10

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

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Preparations for oral administration may be suitably formulated to give controlled release of the active compound

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds for formula (1) may be formulated for parenteral administration by injection e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoule or multi dose containers, e.g. glass vials. The compositions for injection may take  
5 such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use. For particle mediated administration the compounds of  
10 formula (1) may be coated on particles such as microscopic gold particles.

In addition to the formulations described above, the compounds of formula (1) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

15 For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichloro-  
20 fluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

For vaginal or rectal administration the compounds of formula (1) may be formulated as a suppository. These formulations may be prepared by mixing  
25 the active ingredient with a suitable non-irritating excipient which is a solid at room temperature but liquid at the body temperature. Such materials include for example cocoa butter and polyethylene glycols.

The compositions may, if desired, be presented in a pack or dispenser device  
30 which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

- The quantity of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen, and the condition of the patient to be treated. In general, however, daily dosages may range from around 100ng/kg to 100mg/kg e.g. around
- 5 0.01mg/kg to 40mg/kg body weight for oral or buccal administration, from around 10ng/kg to 50mg/kg body weight for parenteral administration and around 0.05mg to around 1000mg e.g. around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.
- 10 The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter. Many of the reactions described are well-known standard synthetic methods which may be applied to a variety of compounds and as such can be used not only to generate compounds of the invention, but also
- 15 where necessary the intermediates thereto.

In the following process description, the symbols  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$  when used in the formulae depicted are to be understood to represent those groups described above in relation to formula (1) unless otherwise indicated. In the

20 reactions described below, it may be necessary to protect reactive functional groups, for example hydroxy, amino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example, Green, T. W. in "Protective Groups in

25 Organic Synthesis", John Wiley and Sons, (1999) and the examples herein]. In some instances, deprotection may be the final step in the synthesis of a compound of formula (1) and the processes according to the invention described hereinafter are to be understood to extend to such removal of protecting groups. It will be appreciated that the syntheses described herein

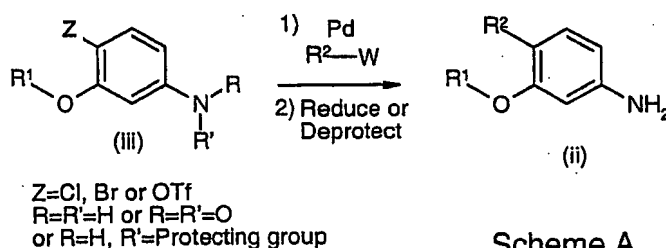
30 for the preparation of compounds of formula (1) also apply to the compounds of formulae (1a), (1b) and (1c), unless otherwise stated.

Compounds of formula (1) may be prepared according to one of several general methods, including the method shown in Scheme D, below.

An appropriate starting material for the preparation of compounds of formula (1) is an amine of formula (ii), as shown below.

5 Amines of general formula (ii) may be prepared in a variety of ways. For example, the amine of formula (ii) where  $R^1$  is a methyl group and  $R^2$  is an oxazole group may be prepared using methods known in the literature (CAS 198821-79-3).

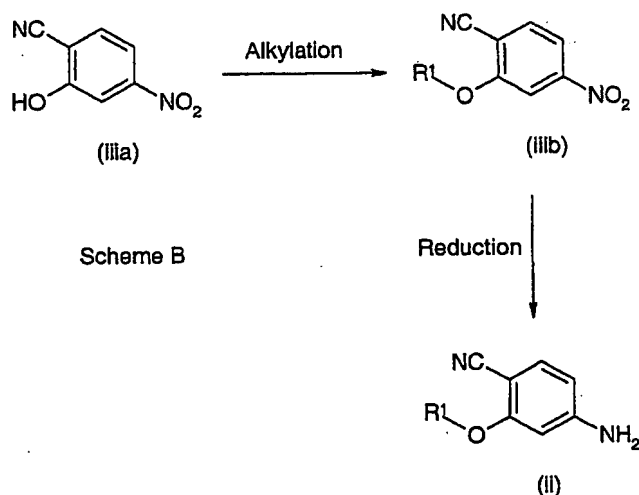
10 Alternatively amines of formula (ii), where  $R^2$  is an optionally substituted heteroaromatic group, may be prepared using the route as shown in Scheme A:



15 For example, a compound of formula (iii), where Z is a halogen atom e.g. Cl or Br or a suitable leaving group e.g. trifluoromethylsulfonyloxy (OTf) and  $-\text{NRR}'$  is a nitro group or an amine group (which may be suitably protected), may be reacted with a derivative of the desired heteroaromatic group ( $\text{R}^2\text{-W}$ , where W is as described below) utilising a palladium catalysed cross coupling reaction. The following literature methodology may be used to perform this coupling reaction according to the nature of the W group; e.g. when W is a hydrogen atom (Heterocycles, 31, pp. 1951-1958, (1990)); the zinc species ( $\text{W}=\text{ZnCl}$ ) (J. Organomet. Chem., 390, pp. 389-398, (1990); Tetrahedron, 53, pp. 7237-7254, (1997) ); the mercury species ( $\text{W}=\text{HgBr}$ ) (Chem. Heterocycl. Compd., 19, pp. 1159-1162, (1983) ) or a boron derivative ( $\text{W}=\text{B}(\text{OH})_2$ ,  $\text{W}=\text{BEt}_2$ ) (J. Med. Chem., 40, pp. 3542-3550, (1997); J. Org. Chem., 63, pp. 8295-8303, (1998) ). The resulting coupled product may require further manipulation, depending on the nature of the  $-\text{NRR}'$  group, in order to obtain an amine of formula (ii). For example, when  $-\text{NRR}'$  is a nitro group this may be reduced to

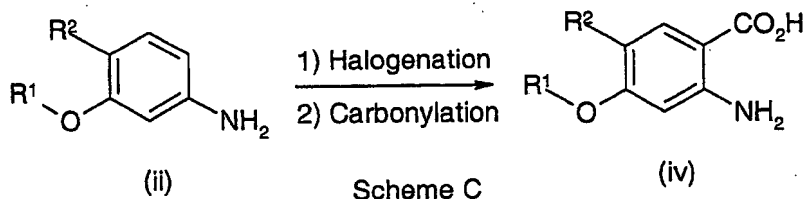
an amine using standard techniques such as those methods as described hereinafter, or when  $-NRR'$  is a protected amine the protecting group may be removed using standard methodology, for example a carbamate protecting group e.g. *tert*-butoxycarbonyl may be removed under acidic conditions e.g. trifluoroacetic acid. It will be appreciated that the various  $R^2-W$  derivatives are either commercially available or may be prepared using methods known to those skilled in the art. In a similar manner the compounds of formula (iii) are either commercially available or may be prepared using methods known to those skilled in the art. For example, the compound of formula (iii) may be prepared by alkylation of the phenol precursor of (iii) using standard techniques.

Further, when  $R^2$  is a CN group amines of formula (ii) may be prepared from 2-hydroxy-4-nitrobenzonitrile (iii*a*) (CAS 39835-14-8) as shown in the general Scheme B below:



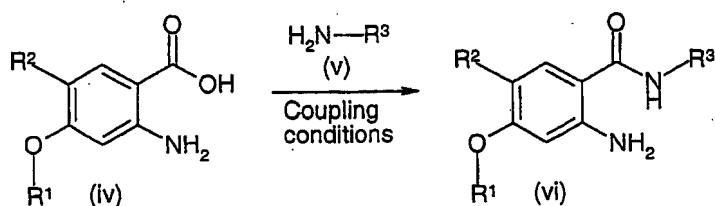
Thus a phenol of formula (iii*a*) may be alkylated using conditions known to those skilled in the art, typically using an alkyl halide e.g. iodoethane and sodium hydride in *N,N*-dimethylformamide, to give an ether of formula (iii*b*). Alternatively these compounds may be commercially available, for example  $R^1=Me$  (CAS 101084-96-2). The compound of formula (iii*b*) may then be reduced to give the desired amine of formula (ii) using standard methods, for example hydrogenolysis using palladium catalysis.

The amine of formula (ii) may then be converted to an amino acid of general formula (iv) using a two-step process as shown in Scheme C. Thus an amine of formula (ii) may be treated with a halogen source such as bromine or a halosuccinimide e.g. chloro or bromosuccinimide. The reaction may be performed in a solvent such as acetonitrile or an ether e.g. a cyclic ether such as tetrahydrofuran at a temperature from about 0° to 30°. When bromine is used as halogen source the reaction may optionally be performed in the presence of added base such as an amine e.g. triethylamine. The intermediate thus formed may be converted into a carboxylic acid of formula (iv) using methods known to those skilled in the art. For example the halogenated intermediate may be treated with carbon monoxide under pressure in the presence of a catalyst e.g. a palladium catalyst such as dichlorobis(triphenylphosphene)palladium(II) in for example water and an appropriate solvent e.g. *N,N*-dimethylformamide or tetrahydrofuran. It may be appropriate to carry out the reaction at an elevated temperature, such as 90-100°C.

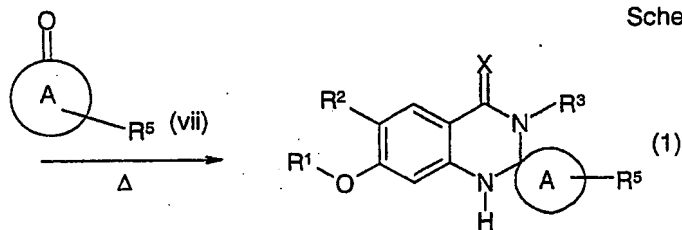


Amino acids of formula (iv) may also be known compounds (e.g. R<sup>1</sup>=Me, R<sup>2</sup>=Oxazole; CAS 371251-38-6).

In one aspect of the invention quinazolinones of formula (1) may be prepared by reacting an amine of formula (vi) with a carbonyl compound of formula (vii). Thus, quinazolinones of formula (1) may be prepared using the general route as shown in Scheme D:



Scheme D



Thus amino acids of formula (iv) may be reacted with amines of formula (v) using coupling reaction conditions familiar to those skilled in the art to give amides (vi). For example, an acid of formula (iv) may be activated *in situ* using for example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), advantageously in the presence of a catalyst such as a *N*-hydroxy compound, e.g. *N*-hydroxybenzotriazole, using suitable conditions, e.g. in *N,N*-dimethylformamide, prior to the subsequent addition of an amine of formula (v). A base such as an amine base e.g. triethylamine or diisopropylethylamine may also be employed in the reaction. Alternatively acids of formula (iv) may be reacted with oxalyl chloride in an inert solvent (such as dichloromethane) to give an intermediate acid chloride, which may or may not be isolated, but which in turn is reacted with an amine of formula (v) at a suitable temperature such as room temperature to give the amide (vi). The reaction may be performed in the presence of a base, such as a hydride, e.g. sodium hydride or an amine, e.g. triethylamine or *N*-methylemorpholine, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane or carbon tetrachloride or an amide, e.g. dimethylformamide at for example ambient temperature.

Amines of formula (v) may be commercially available, known compounds in the literature or may be prepared using methods known to those skilled in the art.



Formation of quinazolinones of formula (1) may be achieved by condensation of amino amides (vi) with aldehydes or ketones of formula (vii) typically using acid, e.g. *p*-toluenesulfonic acid, catalysed conditions similar to those employed by Bhavani and Reddy (Org. Prep. Proced. Int. 1992, 24, 1) or Sharma and Kaur (Synthesis 1989, 9, 677) or Takai *et al* (Chem. Pharm. Bull. 1985, 33, 1116). The acid used as a catalyst may be hydrochloric acid (Klemm *et al*; J. Heterocycl. Chem. 1998, 35, 1269), or acetic acid (Reddy *et al* Indian J. Chem. Sec. B, 1988, 27, 135) or a Lewis acid such as borontrifluoride diethyl etherate. The reaction may be performed in a sealed tube, for example, using microwaves as an energy source or under vacuum. Suitable solvents for use in this reaction include halogenated hydrocarbons, e.g. dichloromethane or dichloroethane, amides, e.g. dimethylformamide, ethers such as cyclic ethers e.g. 1-4-dioxane, alcohols e.g. ethanol or esters e.g. isopropylacetate. Drying agents such as magnesium sulfate or molecular sieves may be added or the reaction may be performed using Dean Stark conditions. The reaction may be achieved at a range of temperatures e.g. from room temperature to reflux.

Carbonyl compounds of formula (vii) are either commercially available or may be prepared using methods known to those skilled in the art. Alternatively a carbonyl compound protected as an acetal may be used in the condensation reaction rather than the carbonyl compound itself. Such compounds are either commercially available or prepared using methods previously reported in the literature.

Compounds of formula (1c) may be prepared from appropriate ketones of formula (vii), e.g. 4-hydroxyproline, using standard methodology known to those skilled in the art, such as those methods as described in the examples hereinafter. For example, starting from 4-hydroxyproline of known stereochemistry, standard manipulations may afford ketones of formula (vii) as enantiomerically pure compounds. Cyclisation of these ketones with amino amides of formula (vi) may thus afford two out of four possible diastereomers of quinazolinones of formula (1c). The diastereomers thus formed may be

separated using methods known to those skilled in the art, such as by column chromatography and/or preparative HPLC.

5 It will be appreciated by one skilled in the art that the group  $R^5$  in compounds of formula (vii) may be further functionalised after ring cyclisation has taken place.

10 Quinazolinethiones of formula (1) (where  $X=S$ ) may be prepared from the corresponding quinazolinone ( $X=O$ ) for example, by reaction with a thiation reagent, such as Lawesson's Reagent or  $P_2S_5$ , in an anhydrous solvent, for example a cyclic ether such as tetrahydrofuran, or toluene at an elevated temperature such as the reflux temperature (see for example Tetrahedron 1985, 41, 5061).

15 It will be appreciated that compounds of formula (1) or any preceding intermediates may be further derivatised by one or more standard synthetic methods employing substitution, oxidation, reduction or cleavage reactions. Particular substitution approaches include conventional alkylation, arylation, heteroarylation, acylation, thioacylation, halogenation, sulphonylation, 20 nitration, formylation and coupling procedures. It will be appreciated that these methods may also be used to obtain or modify other compounds of any of formula (1) or any preceding intermediates where appropriate functional groups exist in these compounds.

25 For example, ester groups may be converted to the corresponding acid [ $-CO_2H$ ] by acid- or base-catalysed hydrolysis depending on the nature of the ester. Acid- or base- catalysed hydrolysis may be achieved for example by treatment with an organic or inorganic acid, e.g. trifluoroacetic acid in an aqueous solvent or a mineral acid such as hydrochloric acid in a solvent such as dioxan or an alkali metal hydroxide, e.g. lithium hydroxide in an aqueous 30 alcohol, e.g. aqueous methanol. Similarly an acid [ $-CO_2H$ ] may be prepared by hydrolysis of the corresponding nitrile [ $-CN$ ], using for example a base such as sodium hydroxide in a refluxing alcoholic solvent, such as ethanol.

In another example, -OH groups may be generated from the corresponding ester or aldehyde [-CHO] by reduction, using for example a complex metal hydride such as lithium aluminium hydride in e.g. tetrahydrofuran or sodium borohydride in an alcohol e.g. methanol. Alternatively an alcohol may be prepared by reduction of the corresponding acid [-CO<sub>2</sub>H], using for example  
5 lithium aluminium hydride in a solvent such as tetrahydrofuran.

Alcohol groups may be converted into leaving groups, such as halogen atoms or sulfonyloxy groups such as an alkylsulfonyloxy, e.g.  
10 trifluoromethylsulfonyloxy or arylsulfonyloxy, e.g. p-toluenesulfonyloxy group using conditions known to those skilled in the art. For example, an alcohol may be reacted with thionyl chloride in a halogenated hydrocarbon e.g. dichloromethane to yield the corresponding chloride. A base e.g. triethylamine may also be used in the reaction.

15 In another example, alcohol or phenol groups may be converted to ether groups by coupling a phenol with an alcohol in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl-, diisopropyl-, or dimethylazodicarboxylate. Alternatively ether groups  
20 may be prepared by deprotonation of an alcohol, using a suitable base e.g. sodium hydride followed by subsequent addition of an alkylating agent, such as an alkylhalide.

Aldehyde or ketone groups may be obtained by oxidation of a corresponding  
25 alcohol using well known conditions. For example using an oxidising agent such as a periodinane e.g. Dess Martin, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane. An alternative oxidation may be suitably activating dimethyl sulfoxide using for example, oxalyl chloride, followed by addition of an alcohol, and subsequent quenching of the reaction by the  
30 addition of an amine base, such as triethylamine. Suitable conditions for this reaction may be using an appropriate solvent, for example, a halogenated hydrocarbon, e.g. dichloromethane at -78°C followed by subsequent warming to room temperature.

In a further example primary amine (-NH<sub>2</sub>) or secondary amine (-NH-) groups may be alkylated using a reductive alkylation process employing an aldehyde or ketone and a borohydride, for example sodium triacetoxymethylborohydride or sodium cyanoborohydride, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane or an alcohol, e.g. ethanol, where necessary in the presence of an acid such as acetic acid at around ambient temperature.

In a further example, amine [-NH<sub>2</sub>] groups may be obtained by hydrolysis from a corresponding imide by reaction with hydrazine in a solvent such as an alcohol, e.g. ethanol at ambient temperature.

In another example, a nitro [-NO<sub>2</sub>] group may be reduced to an amine [-NH<sub>2</sub>], for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as an ether, e.g. tetrahydrofuran or an alcohol e.g. methanol, or by chemical reduction using for example a metal, e.g. tin or iron, in the presence of an acid such as hydrochloric acid.

In a further example amine (-CH<sub>2</sub>NH<sub>2</sub>) groups may be obtained by reduction of nitriles (-CN), for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon, or Raney nickel, in a solvent such as an ether e.g. a cyclic ether, e.g. tetrahydrofuran, at a temperature from -78°C to the reflux temperature.

25

Compounds possessing a urea linker may be prepared by reaction of an isocyanate with an amine in the presence of a base e.g. triethylamine or DIPEA in a suitable solvent such as dichloromethane. Isocyanates may be prepared by reaction of an amine with phosgene or triphosgene in the presence of a base e.g. triethylamine in a suitable solvent such as dichloromethane.

30

Compounds possessing an amide linker may be prepared by reaction of an amine with an activated acid using standard methods known to those skilled in

the art. For example, acids may be activated *in situ* using for example a diimide such as EDC, advantageously in the presence of a catalyst such as a *N*-hydroxy compound, e.g. *N*-hydroxybenzotriazole, using suitable conditions, e.g. in *N,N*-dimethylformamide, prior to the subsequent addition of an amine.

- 5 A base such as an amine base e.g. triethylamine or diisopropylethylamine may also be employed in the reaction. Alternative activated acids, which may be used, include acid chlorides, chloroformates or anhydrides.

- 10 Aromatic halogen substituents in the compounds may be subjected to halogen-metal exchange by treatment with a base, for example a lithium base such as *n*-butyl or *t*-butyl lithium, optionally at a low temperature, e.g. around -78°C, in a solvent such as tetrahydrofuran and then quenched with an electrophile to introduce a desired substituent. Thus, for example, a formyl group may be introduced by using dimethylformamide as the electrophile; a  
15 thiomethyl group may be introduced by using dimethyldisulphide as the electrophile. Aromatic halogen substituents may also be subjected to palladium catalysed reactions, to introduce, for example, acid, ester, cyano or amino substituents.

- 20 In another example, sulfur atoms in the compounds, for example when present in a linker group  $L^1$ ,  $L^2$  or  $L^3$  may be oxidised to the corresponding sulfoxide or sulfone using an oxidising agent such as a peroxy acid, e.g. 3-chloroperoxybenzoic acid, in an inert solvent such as a halogenated hydrocarbon, e.g. dichloromethane, at around ambient temperature.

- 25 N-oxides of compounds of formula (1) may be prepared for example by oxidation of the corresponding nitrogen base using an oxidising agent such as hydrogen peroxide in the presence of an acid such as acetic acid, at an elevated temperature, for example around 70°C to 80°C, or alternatively by  
30 reaction with a peracid such as peracetic acid in a solvent, e.g. dichloromethane, at ambient temperature.

Salts of compounds of formula (1) may be prepared by reaction of a compound of formula (1) with an appropriate base or acid in a suitable solvent

or mixture of solvents e.g. an organic solvent such as an ether e.g. diethylether, or an alcohol, e.g. ethanol or an aqueous solvent using conventional procedures. Salts of compounds of formula (1) may be exchanged for other salts by use of conventional ion-exchange chromatography procedures.

Where it is desired to obtain a particular enantiomer of a compound of formula (1) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers.

10

Thus for example diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (1) e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by crystallisation and the desired enantiomer recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt.

15

In another resolution process a racemate of formula (1) may be separated using chiral High Performance Liquid Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above.

20

Chromatography, recrystallisation and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular geometric isomer of the invention.

25

The following Examples illustrate the invention. All temperatures are in °C. Where experimental detail is not given for the preparation of a reagent it is either commercially available, or it is known in the literature, for which the CAS number is quoted. <sup>1</sup>H NMR spectra were obtained at 300MHz or 400MHz unless otherwise indicated.

30

The following LCMS conditions were used to obtained the retention times (RT) as described herein:

**LCMS conditions:**

HP1100 (Diode Array) linked to a Finnigan LC-Q Mass Spectrometer, ESI mode with Pos/Neg ionization

5 Column: Luna C18(2) 100×4.6mm, 5µm particle size  
Analytical column  
Column Temp: 35°C  
Mobile Phase: A: Water + 0.08% formic acid  
B: Acetonitrile + 0.08% formic acid  
Flow rate: 3ml/min  
10 Gradient: Time (mins): % Composition B:  
0 5  
4.4 95  
5.30 95  
5.32 5  
15 6.5 5  
Run time: 6.5 mins  
Typical Injection Vol: 10µl  
Detector Wavelength: DAD 200-400nm

**20 Chiral column conditions:**

Varian Gradient HPLC system consisting of Varian 9012/9050/9100 Modules and Waters fraction collector.

Column: Chiralpak® AD 250× 20mm, 10µm particle size Prep column  
25 Column Temp: 35°C  
Mobile Phase: A: EtOH + 0.1% DEA  
B: Heptane  
Flow rate: 6ml/min  
Isocratic: 60% A : 40% B  
30 Run time: 18 mins  
Typical Injection Vol: 320µl at 40mg/ml  
Detector Wavelength: 252nm

**Preparative LC conditions (Method A):**

35 Gilson 215 liquid handler setup.

Column: Luna C18(2) 250×21.2mm, 5µM particle size PREP column  
Column Temp: Ambient  
Gradient: Variable – depends on retention time of sample in LC-MS analysis.  
40 Run Time: 20 mins  
Flow rate: 25ml/min  
Typical Injection Vol: 0.5 – 4.0ml at 25mg/ml  
Detector Wavelength: 210 and 254nm  
Mobile Phase: A: Water + 0.08% formic acid  
45 B: Acetonitrile + 0.08% formic acid

**Preparative LC conditions (Method B):**

Gilson 215 liquid handler setup.

5 Column: Luna C18(2) 100x21mm, 5  $\mu$ M particle size Prep column  
 Column Temp: Ambient.  
 Gradient: Variable- depends on retention of sample in LCMS screen  
 Run Time: 10 mins  
 10 Flow rate: 20ml/min  
 Typical Injection volume: 500  $\mu$ l  
 Detector Wavelength: 210 and 254nm  
 Mobile phase: A: Water + 0.08% formic acid  
 B: MeCN + 0.08 % formic acid

15

**Retrieve medium pressure liquid chromatography (MPLC) conditions:**

Column: Redisep Isco Flash Column (4g)  
 Gradient: Variable – depends on  $R_f$  of sample.  
 Flow rate: Approximately 18ml/min

20

Abbreviations used :-

DCM – Dichloromethane; DCE – Dichloroethane;  
 DEA – Diethylamine; Et<sub>2</sub>O - Diethyl ether;  
 DMF - *N,N*-Dimethylformamide; d<sub>6</sub>-DMSO - Dimethyl-d<sub>6</sub> sulphoxide;  
 25 DIPEA - Di-*iso*-propylethylamine; EtOH – Ethanol;  
 EtOAc - Ethyl acetate; MeOH – Methanol;  
 d<sub>4</sub>-MeOH - Methanol-d<sub>4</sub>; TEA – Triethylamine;  
 PTSA - *para*-Toluenesulfonic acid  
 BOC – *tert*-butoxycarbonyl HOBT - 1-Hydroxybenzotriazole hydrate;  
 30 EDC - 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride  
 HBTU - 2-[1*H*-Benzotriazole-1-yl]-1,1,3,3-tetramethyluronium  
 hexafluorophosphate  
 DBN - 1,8-diazobicyclo[4.3.0]non-5-ene

35

**Intermediate 1.****2-Amino-4-methoxy-*N*-methyl-5-oxazol-5-yl-benzamide**

To a solution of 2-amino-4-methoxy-5-oxazol-5-yl-benzoic acid (CAS 371251-38-6) (200mg) in dry DCM (10ml) at room temperature was added TEA



(0.33ml) and EDC (250mg) followed by methylamine hydrochloride (130mg). The reaction mixture was allowed to stir for 22 hours. The solvent was removed *in vacuo* and the residue purified by column chromatography on silica eluting with EtOAc to yield the title compound as a pale yellow solid  
5 (76mg, 36%). TLC  $R_f$  0.31 (EtOAc). LCMS 248  $[M+H]^+$ , RT 2.04 mins.  $^1H$  NMR 300MHz ( $d_6$ -DMSO) 8.33 (1H, s), 8.25-8.20 (1H, m, br), 7.85 (1H, s), 7.25 (1H, s), 6.95-6.85 (2H, s, br), 6.40 (1H, s), 3.85 (3H, s), 2.75-2.70 (3H, d).

### Intermediate 2.

#### 10 2-Amino-4-methoxy-5-oxazol-5-yl-benzamide

2-Amino-4-methoxy-5-oxazol-5-yl-benzoic acid (CAS 371251-38-6) (3.5g), EDC (2.87g) and HOBt (2.02g) were combined in a 0.5M ammonia in dioxane solution (100ml) and stirred at room temperature for 21 hours. The reaction mixture was evaporated directly onto silica and purified by column  
15 chromatography on silica eluting with 75-100% EtOAc/heptane rising to 5% MeOH/EtOAc to give the title compound as a yellow solid (1.90g, 55%). TLC  $R_f$  0.15 (75% EtOAc/Heptane). LCMS 234  $[M+H]^+$ , RT 1.95 mins.  $^1H$  NMR 300MHz ( $d_6$ -DMSO) 8.36 (1H, s), 7.94 (1H, s), 7.85 (1H, s, br), 7.30 (1H, s), 7.05 (3H, s, br), 6.45 (1H, s), 3.91 (3H, s).

#### 20 Intermediate 3.

#### *tert*-Butyl-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[piperidine-4,2'-quinazoline]-1-carboxylate

To a stirred solution of Intermediate 1 (270mg),  $MgSO_4$  (500g) and PTSA (1.0mg) in DCM (10 ml) under nitrogen was added *tert*-butyl 4-oxo-1-piperidinecarboxylate (218mg). The reaction mixture was heated to 60°C for 12  
25 hours, allowed to cool and then filtered. The filtrate was concentrated *in vacuo* and the residue dissolved in DCM (100ml) and washed with aqueous 1M aqueous HCl (30ml), aqueous  $Na_2CO_3$  (30ml) and water (30ml). The organic layer was separated, dried over  $MgSO_4$ , filtered and concentrated *in vacuo*.  
30 The residue was purified by recrystallisation from EtOAc,  $Et_2O$  and heptane to yield the title compound as a yellow solid (386mg, 90%). TLC  $R_f$  0.65 (EtOAc). LCMS 429  $[M+H]^+$ , RT 3.20 mins.  $^1H$  NMR 300MHz ( $d_6$ -DMSO) 8.35 (1H, s),

8.00 (1H, s), 7.33 (2H, s), 7.18 (1H, s), 6.71 (1H, s), 3.93 (3H, s), 3.93-3.83 (2H, m), 3.25-3.03 (2H, m), 2.95 (3H, s), 2.00-1.80 (4H, m), 1.42 (9H, s).

#### **Intermediate 4.**

##### **(2-Oxo-indan-5-yl)-carbamic acid *tert*-butyl ester**

- 5 5-Nitro-2-indanone (100mg), di-*tert*-butyldicarbonate (135mg), palladium on carbon (15mg), 3A powdered molecular sieves (30mg) and THF (10ml) were combined in a Parr vessel, which was purged with hydrogen gas at 100psi and heated to 50°C for 12.5 hours. The mixture was filtered through a pad of celite, washing through with THF. The solvent was removed *in vacuo* and the
- 10 residue triturated with diethyl ether to yield the title compound as a mustard coloured solid (66mg, 48%). TLC R<sub>f</sub> 0.59 (EtOAc/heptane). <sup>1</sup>H NMR 300MHz (d<sub>6</sub>-DMSO) 9.12 (1H, s, br), 7.27 (1H, s), 7.06 (1H, d), 6.97 (1H, d), 3.3 (2H, s), 3.24 (2H, s), 1.27 (9H, s).

#### **Intermediate 5.**

- 15 **7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1'H-spiro[pyrrolidine-3,2'-quinazolin]-4'(3'H)-one formate salt**

- tert*-Butyl-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxylate (536mg) and formic acid (3ml) were combined and stirred at room temperature overnight. The
- 20 mixture was concentrated carefully *in vacuo* and the resulting residue washed sparingly with DCM to afford the title compound as a solid (490mg, 72%).
- LCMS 315 [M+H]<sup>+</sup>, RT 1.32 mins.

#### **Intermediate 6.**

- Methyl 2-(2-([(benzyloxy)carbonyl]amino)ethyl)-7-methoxy-3-methyl-6-(1,3-oxazol-5-yl)-4-oxo-1,2,3,4-tetrahydroquinazoline-2-carboxylate**
- 25

- To a solution of Intermediate 1 (128mg) in isopropyl acetate (50ml) were added methyl 4-([(benzyloxy)carbonyl]amino)-2-oxobutanoate (CAS 81323-56-0). (137mg) and PTSA (catalytic). The solution was stirred overnight at 95°C. The reaction mixture was evaporated directly onto silica and purified by
- 30 column chromatography eluting with EtOAc to give the title compound as a tan solid (158mg, 61%). TLC R<sub>f</sub> 0.23 (100% EtOAc). LCMS 495 [M+H]<sup>+</sup>, RT 3.16 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOD) 8.20 (1H, s), 8.10 (1H, s), 7.35-7.20

(6H, m), 6.40 (1H, s), 5.10 (2H, s), 4.10 (1H, s), 3.95 (3H, s), 3.65 (3H, s), 3.55-3.25 (2H, m), 3.15 (3H, s), 2.45-2.25 (2H, m).

#### Intermediate 7.

##### iso-Propyl-(4R)-4-hydroxy-D-prolinate hydrochloride

5 To a suspension of *cis*-4-hydroxy-D-proline (1.0g) in dry iso-propanol (25ml) under nitrogen cooled to 0°C was added dropwise thionyl chloride (0.8ml). The reaction mixture was heated at 100°C for 6 hours. The mixture was concentrated *in vacuo* to afford the title compound as a white solid (1.6g, quantitative). <sup>1</sup>H NMR 400MHz (d<sub>4</sub>-MeOH) 5.17-5.08 (1H, hep), 4.52-4.47  
10 (2H, m), 3.40-3.32 (2H, m), 2.48-2.41 (1H, m), 2.36-2.32 (1H, m), 1.33-1.30 (6H, d).

#### Intermediate 8.

##### 1-tert-Butyl 2-isopropyl-(2R,4R)-4-hydroxy-pyrrolidine-1,2-dicarboxylate

To a solution of Intermediate 7 (0.8g) in dioxane / H<sub>2</sub>O (10ml / 10ml) cooled to  
15 0°C was added di-*tert*-butyl dicarbonate (0.91g) followed by TEA (1.2ml) dropwise. The reaction mixture was allowed to warm to room temperature and stirred overnight. The dioxane was removed *in vacuo* and the residue diluted with DCM / H<sub>2</sub>O (150ml / 50ml). The organic layer was separated, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to afford the title compound as a  
20 colourless oil (1.1g, quantitative). <sup>1</sup>H NMR 400MHz (CDCl<sub>3</sub>) 5.11-5.04 (1H, hep), 4.36-4.23 (2H, m), 3.73-3.48 (2H, m), 3.36-3.33 (1H, d), 2.38-2.26 (1H, m), 2.09-2.02 (1H, m), 1.46 and 1.43 (9H, 2xs), 1.32-1.24 (6H, m).

#### Intermediate 9.

##### 1-tert-Butyl 2-isopropyl-(2R)-4-oxopyrrolidine-1,2-dicarboxylate

25 To a solution of oxalyl chloride (0.53ml) in dry DCM (15ml) cooled to -78°C was added dropwise dry DMSO (0.43ml). After stirring at -78°C for 15 mins, a solution of Intermediate 8 (1.1g) in dry DCM (15ml) was added slowly and the mixture stirred at -78°C for another 40 mins. Dropwise addition of TEA (2.8ml) then took place and the reaction mixture was allowed to warm to 0°C and  
30 stirred for 60 mins. The reaction mixture was diluted with H<sub>2</sub>O (20ml) and extracted with DCM (100ml). The organic layer was separated, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. Purification of the residue by column chromatography on silica eluting with 20% EtOAc/Heptane afforded

the title compound as a yellow oil (0.58, 53%). TLC R<sub>f</sub> 0.76 (50% EtOAc/Hexane). <sup>1</sup>H NMR 400MHz (CDCl<sub>3</sub>) 5.10-54.98 (1H, hep), 4.77-4.62 (1H, m), 3.93-3.83 (2H, m), 3.00-2.84 (1H, m), 2.57-2.50 (1H, dd), 1.46 (9H, s), 1.27-1.24 (6H, d).

5

### Example 1.

#### 7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1'H-spiro[cyclohexane,2'-quinazolin]-4'(3'H)-one

To a stirred solution of 2-amino-4-methoxy-*N*-methyl-5-oxazol-5-yl-benzamide (150mg), MgSO<sub>4</sub> (500mg) and PTSA (1.0mg) in DCM (10ml) under nitrogen was added cyclohexanone (60mg). The reaction mixture was heated to 60°C for 12 hours, allowed to cool and then filtered. The filtrate was concentrated *in vacuo* and the residue taken up in DCM (100ml) and washed with aqueous 1M HCl (30ml), aqueous Na<sub>2</sub>CO<sub>3</sub> (30ml), water (30ml). The organic layer was separated, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by trituration with EtOAc to afford the title compound as a pale yellow solid (120mg, 60%). TLC R<sub>f</sub> 0.48 (EtOAc). LCMS 328 [M+H]<sup>+</sup>, RT 2.95 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.19 (1H, s), 8.15 (1H, s), 7.35 (1H, s), 6.67 (1H, s), 4.03 (3H, s), 3.08 (3H, s), 2.10-2.00 (2H, m), 1.95-1.82 (2H, m), 1.80-1.60 (5H, m), 1.60-1.41 (1H, m).

20

Examples 2-6 were prepared in a similar manner to the method of Example 1:-

### Example 2.

#### 7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1'H-spiro[cyclopentane,2'-quinazolin]-4'(3'H)-one

From Intermediate 1 (70mg) and cyclopentanone (24mg). The residue was purified by preparative HPLC (Method A) to yield the title compound as a pale yellow solid (13mg, 15%). TLC R<sub>f</sub> 0.36 (EtOAc). LCMS 314 [M+H]<sup>+</sup>, RT 2.68 mins. <sup>1</sup>H NMR 300MHz (d<sub>6</sub>-DMSO) 8.34 (1H, s), 7.97 (1H, s), 7.32 (1H, s), 7.24 (1H, s), 6.47 (1H, s), 3.95 (3H, s), 2.92 (3H, s), 2.12-1.99 (2H, m), 1.85-1.61 (6H, m).

30

### Example 3.

**7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-2,3,5,6-tetrahydro-1'H-spiro[pyran-4,2'-quinazolin]-4'(3'H)-one**

From Intermediate 1 (100mg) and tetrahydro-2H-pyran-4-one (80mg). The residue was purified by column chromatography on silica eluting with 0-5% MeOH/DCM to yield the title compound as a cream solid (68mg, 51%). TLC R<sub>f</sub> 0.48 (10%MeOH/DCM). LCMS 330 [M+H]<sup>+</sup>, RT 2.30 mins. <sup>1</sup>H NMR 300MHz (d<sub>6</sub>-DMSO) 8.31 (1H, s), 7.96 (1H, s), 7.30 (2H, s), 6.69 (1H, s), 3.95 (3H, s), 3.85-3.68 (4H, m), 2.98 (3H, s), 2.18-2.02 (2H, m), 1.83-1.72 (2H, m).

**Example 4.**

10 **7'-Methoxy-3'-methyl-4-methyl-6'-(1,3-oxazol-5-yl)-1'H-spiro[piperidine-4,2'-quinazolin]-4'(3'H)-one**

From Intermediate 1 (100mg) and N-methyl-4-piperidone (0.056ml). The residue was purified by trituration with Et<sub>2</sub>O to yield the title compound as a cream solid (60mg, 43%). TLC R<sub>f</sub> 0.21 (10%MeOH/DCM). LCMS 343 [M+H]<sup>+</sup>, RT 1.42 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.22 (1H, s), 8.20 (1H, s), 7.36 (1H, s), 6.65 (1H, s), 4.02 (3H, s), 3.20 (3H, s), 3.92-3.80 (2H, m), 2.54-2.35 (2H, m), 2.36 (3H, s), 2.27-2.14 (2H, m), 2.10-1.96 (2H, m).

**Example 5.**

20 **3-Benzyl-7'-methoxy-3'-methyl-4-methyl-6'-(1,3-oxazol-5-yl)-1'H-spiro[pyrrolidine-3,2'-quinazolin]-4'(3'H)-one**

From Intermediate 1 (406mg) and 1-benzyl-3-pyrrolidinone (288mg). The residue was purified by column chromatography on silica eluting with 5-10% MeOH/DCM to yield the title compound as a black solid (150mg, 23%). TLC R<sub>f</sub> 0.6 (10%MeOH/DCM). LCMS 405.2 [M+H]<sup>+</sup>, RT 1.73 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.23 (1H, s), 8.15 (1H, s), 7.48-7.30 (6H, m), 6.46 (1H, s), 4.02 (3H, s), 3.95-3.74 (2H, bdd), 3.27-3.16 (1H, m), 3.20 (3H, s), 3.08-2.82 (3H, m), 2.64-2.46 (1H, m), 2.32-2.18 (1H, m).

**Example 6.**

30 **7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1,3-dihydro-1'H-spiro[indene-2,2'-quinazolin]-4'(3'H)-one**

From Intermediate 1 (50mg) and 2-indanone (27mg). The residue was purified by trituration with EtOAc:Et<sub>2</sub>O (5:1) to yield the title compound as a pale yellow solid (28mg, 38%). TLC R<sub>f</sub> 0.7 (10%MeOH/DCM). LCMS 362 [M+H]<sup>+</sup>, RT

3.31 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.24 (2H, s), 7.37 (1H, s), 7.33-7.22 (5H, m), 6.40 (1H, s), 3.98 (3H, s), 3.72 (2H, d), 3.34 (2H, d), 3.13 (3H, s).

**Example 7.**

**7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4,5-dihydro-1'H-spiro[furan-3,2'-quinazolin]-4'(3'H)-one**

To a stirred solution of Intermediate 1 (50mg), MgSO<sub>4</sub> (0.5g) and PTSA (1.0mg) in DCE (10ml) under nitrogen was added dihydrofuran-3-one (CAS 22929-52-8) (80mg). The reaction mixture was heated to 91°C for 8 hours and allowed to cool. The reaction mixture was taken up in EtOAc (100ml) and washed with aqueous NaHCO<sub>3</sub> (20ml). The organic layer was separated, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was taken up in DCM (5ml), filtered and the filtrate concentrated *in vacuo* and purified by trituration with MeOH:Et<sub>2</sub>O (1:20) to afford the title compound as a solid (8mg, 13%). TLC R<sub>f</sub> 0.45 (EtOAc). LCMS 316 [M+H]<sup>+</sup>, RT 2.26 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.25 (1H, s), 8.20 (1H, s), 7.40 (1H,s), 6.50 (1H,s), 4.17 (1H,d), 4.13-3.95 (2H,m), 4.03 (3H,s), 3.73 (1H,d), 3.15 (3H,s), 2.65-2.55 (1H,m), 2.35-2.22 (1H,m).

**Example 8.**

**tert-Butyl-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxylate**

To a stirred solution of Intermediate 1 (800mg) in DCE (20 ml) under nitrogen was added 1-N-Boc-3-pyrrolidinone (600mg). The reaction mixture was heated to 91°C for 14 hours and allowed to cool. The reaction mixture was taken up in EtOAc (100ml) and washed with aqueous Na<sub>2</sub>CO<sub>3</sub> (40ml) and aqueous 1M HCl (40ml). The organic layer was separated, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to yield the title compound as a brown solid (1.15 g, 86%). TLC R<sub>f</sub> 0.48 (EtOAc). LCMS 415 [M+H]<sup>+</sup>, RT 3.05 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.19 (1H, s), 8.18 (1H, s), 7.37 (1H,s), 6.50 (1H,s), 4.00 (3H,s), 3.72-3.58 (4H,m), 3.12 (3H,s), 2.75-2.55 (1H,m), 2.32-2.12 (1H,m), 1.52 and 1.47 (9H, 2xd).

**Example 8a.**

**Enantiomer 1 of tert-Butyl-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxylate**

Example 8 (80mg) was separated into its component enantiomers on a chiral pak column eluting with 3:1 A:B (A = EtOH + 10.1% DEA) (B=Heptane). This gave enantiomer 1 as a solid (32 mg, 80%). Chiral LC RT 5.89 mins. LCMS 415 [M+H]<sup>+</sup>, RT 3.05 mins.

5 **Example 8b.**

**Enantiomer 2 of *tert*-Butyl-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1*H*,1'*H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxylate**

10 Example 8 (80mg) was separated into its component enantiomers on a chiral pak column eluting with 3:1 A:B (A = EtOH + 10.1% DEA) (B=Heptane). This gave enantiomer 2 as a solid (34 mg, 85%). Chiral LC RT 7.14 mins. LCMS 415 [M+H]<sup>+</sup>, RT 3.05 mins.

**Example 9.**

15 ***tert*-Butyl 7'-methoxy-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1*H*,1'*H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxylate**

To a stirred solution of Intermediate 2 (360mg) in DCE (20 ml) under nitrogen was added 1-*N*-Boc-3-pyrrolidinone (286mg). The reaction mixture was heated to 80°C for 3.5 hours and allowed to cool. The reaction mixture was taken up in EtOAc (100ml) and washed with aqueous Na<sub>2</sub>CO<sub>3</sub> (30ml) and  
20 aqueous 1M HCl (30ml). The organic layer was separated, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to yield the title compound (579mg, 94%). TLC R<sub>f</sub> 0.22 (5%MeOH/DCM). LCMS 401 [M+H]<sup>+</sup>, RT 3.25 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.20 (1H, s), 8.18 (1H, s), 7.37 (1H, s), 6.48 (1H, s) 4.00 (3H, s), 3.58 (2H, m), 3.55 (2H, m), 2.25 (2H, m), 1.50 (9H, 2xs).

25 **Example 10.**

***tert*-Butyl [7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-1,3,3',4'-tetrahydro-1'*H*-spiro[indene-2,2'-quinazolin]-5-yl]carbamate**

To a stirred solution of Intermediate 1 (23mg) in DCE (4 ml) under nitrogen was added Intermediate 4 (66mg). The reaction mixture was heated at reflux  
30 for 18 hours and allowed to cool. The solvent was removed *in vacuo* and the residue purified by column chromatography on silica eluting with 70% EtOAc/heptane. The product was further purified by trituration with DCM/pentane to yield the title compound as a sandy coloured solid (14mg, 33%). TLC R<sub>f</sub> 0.59 (EtOAc). LCMS 477 [M+H]<sup>+</sup>, RT 3.60 mins. <sup>1</sup>H NMR

300MHz (d<sub>6</sub>-DMSO) 9.30 (1H, s, br), 8.34 (1H, s), 8.00 (1H, s), 7.5 (1H, s), 7.4 (1H,s), 7.3 (1H, s), 7.2 (1H, d), 7.1 (1H, d), 6.4 (1H, s), 3.85 (3H, s), 3.5 (2H, m), 3.1 (2H, m), 2.85 (3H, s), 1.45 (9H, s).

**Example 11.**

5 **7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-2,3-dihydro-1'H-spiro[indene-1,2'-quinazolin]-4'(3'H)-one**

To a stirred solution of Intermediate 1 (50mg) and PTSA (1.0mg) in DMF (2 ml), was added 1-indanone (80mg). The reaction mixture was heated to 170°C for 30 mins in a microwave reactor and allowed to cool. The reaction  
10 mixture was concentrated *in vacuo* and the residue purified by preparative HPLC (Method A) to afford the title compound as a solid (27.8mg, 38%). HPLC: RT 3.20 mins. LCMS: 362 [M+H]<sup>+</sup>, RT 3.25 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.23 (1H, s), 8.08 (1H, s), 7.50-7.45 (1H,d), 7.35-7.25 (4H,m), 6.33 (1H,s), 3.95 (3H, s), 3.09-3.02 (2H,m), 2.76 (3H,s), 2.00-2.45 (2H,m).

15 **Example 12.**

**7'-Methoxy-3'-methyl-5-nitro-6'-(1,3-oxazol-5-yl)-1,3-dihydro-1'H-spiro[indene-2,2'-quinazolin]-4'(3'H)-one**

To a stirred solution of Intermediate 1 (200mg) and PTSA (1.0mg) in DMF (5 ml) was added 5-nitro-2-indanone (430mg). The reaction mixture was heated  
20 to 110°C for 30 mins in a microwave reactor and allowed to cool. The solvent was removed *in vacuo* and the residue purified by column chromatography on silica eluting with 70% EtOAc/heptane followed by 5% MeOH/DCM to afford the title compound as a brown solid (252mg, 77%). TLC R<sub>f</sub> 0.68 (EtOAc). LCMS 407 [M+H]<sup>+</sup>, RT 3.15 mins. <sup>1</sup>H NMR 300MHz (d<sub>6</sub>-DMSO) 8.55 (1H, s),  
25 8.17 (1H, s), 8.15 (1H, dd), 8.05 (1H, s), 7.65 (1H, s), 7.55 (1H,d), 7.35 (1H, s), 6.37 (1H,s), 3.9 (3H, s), 3.8 (1H, d), 3.7 (1H,d), 3.35 (1H,d), 3.27 (1H,d), 2.95 (3H,s).

**Example 13.**

30 **5-Amino-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1,3-dihydro-1'H-spiro[indene-2,2'-quinazolin]-4'(3'H)-one**

Example 12 (246mg) and palladium on carbon were combined in EtOH (15ml) and stirred under hydrogen gas for 48 hours. The reaction mixture was filtered through a pad of celite and the filtrate concentrated *in vacuo*. The resulting residue was dissolved in DCM (30ml) and washed with aqueous 1M



HCl (2x15ml). The aqueous layers were collected and extracted with DCM (3x30ml). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and the solvent removed *in vacuo*. The resulting residue was purified by column chromatography on silica eluting with 50-100% EtOAc/heptane to yield the  
5 title compound as a yellow solid (12.9 mg, 56%). TLC R<sub>f</sub> 0.42 (EtOAc). LCMS: 377 [M+H]<sup>+</sup>, RT 1.78 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.23 (1H, s), 8.23 (1H, s), 7.37 (1H, s), 7.00 (1H, d), 6.70 (1H, s), 6.65 (1H, d), 6.43, 4.00 (3H, s), 3.57 (2H, m), 3.23 (2H, m), 3.05 (3H, s).

10 Examples 14-15 were prepared in a similar manner to the method of example 12:-

**Example 14.**

**7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4,6-dihydro-1'H-spiro[cyclopenta[b]thiophen-5,2'-quinazolin]-4'(3'H)-one**

15 From Intermediate 1 (100mg) and 4,6-dihydrocyclopenta[b]thiophen-5-one (CAS 33449-51-3) (270mg). The residue was purified by column chromatography on silica eluting with 75% EtOAc/heptane followed by trituration with DCM/Et<sub>2</sub>O to yield the title compound as an off-white solid (34mg, 23%). R<sub>f</sub> 0.62 (EtOAc). LCMS 368 [M+H]<sup>+</sup>, RT 3.14 mins. <sup>1</sup>H NMR  
20 300MHz (d<sub>6</sub>-DMSO) 8.35 (1H, s), 8.0 (1H, s), 7.8 (1H,s), 7.48 (1H, d), 7.32 (1H, s), 6.95 (1H, d), 6.4 (1H, s), 3.9 (3H, s), 3.5 (2H, m), 3.1 (2H,m), 2.9 (3H, s).

**Example 15.**

**7-Methoxy-3-methyl-6-(1,3-oxazol-5-yl)-4',5'-dihydro-1'H-spiro[quinazoline-2,3'-thiophen]-4(3'H)-one**

25 From Intermediate 1 (200mg) and tetrahydrothiophen-3-one (0.37ml). The residue was purified by column chromatography on silica eluting with 75-100% EtOAc/heptane followed by trituration with DCM/Et<sub>2</sub>O to yield the title compound as an off-white solid (200mg, 78%). TLC R<sub>f</sub> 0.38 (EtOAc). LCMS  
30 332 [M+H]<sup>+</sup>, RT 2.74 mins. <sup>1</sup>H NMR 300MHz (d<sub>6</sub>-DMSO) 8.35 (1H, s), 8.0 (1H, s), 7.38 (1H, s), 7.29 (1H, s), 6.62 (1H, s), 3.95 (3H, s), 3.15 (1H, d), 3.1 (1H,m), 3.05 (3H, s), 2.95 (1H, m), 2.85 (1H, d), 2.45 (1H, m), 2.2 (1H, m).

**Example 16.**

**(3R)-7'-Methoxy-3,3'-dimethyl-6'-(1,3-oxazol-5-yl)-1'H-spiro[cyclopentane-1,2'-quinazolin]-4'(3'H)-one**

To a stirred solution of Intermediate 1 (100mg) and PTSA (1.0mg) in DMF (3ml) was added (*R*)-(+)-3-methyl cyclopentanone (0.1ml). The reaction mixture was heated to 150°C for 30 mins in a microwave reactor and allowed to cool. The solvent was removed *in vacuo* and the residue purified by preparative HPLC (Method A) to afford the title compound as a beige solid (13mg, 10%). LCMS 328 [M+H]<sup>+</sup>, RT 3.10 mins. <sup>1</sup>H NMR 300MHz (d<sub>6</sub>-DMSO) 8.3 (1H, s), 7.9 (1H, s), 7.3 (1H, s), 7.25 (1H, s), 6.4 (1H, s), 3.9 (3H, s), 2.9 (3H, s), 2.4-2.25 (1H, m), 2.2-1.7 (4H, m), 1.5-1.2 (2H, m), 1.0 (3H, m).

**Example 17.**

**Ethyl 7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1'H-spiro[cyclopentane-1,2'-quinazoline]-3-carboxylate**

Intermediate 1 (123mg), acetic acid (10ml) and ethyl 3-oxocyclopentane-1-carboxylate (135mg) were combined and heated to 70°C under a slight vacuum for 2 hours. After cooling to room temperature the solvent was removed *in vacuo* and the residue purified by column chromatography on silica to afford the title compound as an off-white solid (154mg, 81%). TLC R<sub>f</sub> 0.525 (20% EtOH / EtOAc). LCMS 386 [M+H]<sup>+</sup>, RT 2.95 mins. <sup>1</sup>H NMR 300MHz (d<sub>6</sub>-DMSO) 8.35 (1H, s), 7.95 (1H, 2 x s), 7.35 (2H, s), 6.45 (1H, d), 4.1 (2H, m), 3.9 (3H, 2 x s), 3.1-2.9 (4H, m), 2.4-1.8 (4H, m), 1.4-1.1 (5H, m).

**Example 18.**

**7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1'H-spiro[cyclopentane-1,2'-quinazoline]-3-carboxylic acid**

Example 17 (145mg), LiOH.H<sub>2</sub>O (24mg), THF (5ml) and H<sub>2</sub>O (1ml) were combined and stirred at room temperature for 18 hours. The solvents were removed *in vacuo* and the residue partitioned between 1M HCl (20ml) and EtOAc (20ml). The EtOAc layer was dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to afford the title compound as a yellow solid (112mg, 84%). LCMS 358 [M+H]<sup>+</sup>, RT 2.24 mins. <sup>1</sup>H NMR 300MHz (d<sub>6</sub>-DMSO) 12.3 (1H, br s), 8.3 (1H, s), 7.95 (1H, 2 x s), 7.3 (2H, m), 6.4 (1H, d), 3.9 (3H, 2 x s), 3.0-2.8 (4H, m), 2.35-1.75 (6H, m).

**Example 19.**

**7-Methoxy-3-methyl-6-(1,3-oxazol-5-yl)-4',5'-dihydro-1'H-spiro[quinazoline-2,3'-thiophen]-4(3'H)-one-1',1'-dioxide**

To a solution of Example 15 in methanol (10ml) was added a solution of oxone® in H<sub>2</sub>O (5ml) and the reaction mixture stirred at room temperature for 18 hours. The solvent was removed *in vacuo*. The residue was purified by trituration with H<sub>2</sub>O and washing with Et<sub>2</sub>O followed by further trituration with MeOH/DCM to yield the title compound as an off-white solid (26mg, 24%). LCMS 364 [M+H]<sup>+</sup>, RT 2.22 mins. <sup>1</sup>H NMR 300MHz (d<sub>6</sub>-DMSO) 8.3 (1H, s), 8.0 (1H, s), 7.8 (1H, s), 7.35 (1H, s), 6.47 (1H, s), 3.92 (3H, s), 3.4 (4H, m), 3.0 (3H, s), 2.75 (1H, m), 2.55 (1H, m).

**Example 20.**

**7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1'H-spiro[piperidine-4,2'-quinazolin]-4'(3'H)-one**

Formic acid (3ml) and Intermediate 3 (0.25g) were stirred at room temperature for 2 hours. The reaction mixture was concentrated *in vacuo* and taken up in aqueous 1M HCl (25ml) and washed with Et<sub>2</sub>O (50ml). The aqueous solution was basified with aqueous 1M NaOH and extracted with EtOAc (50ml). The organic layer was separated, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to yield the title compound as a white solid (130mg, 68%). LCMS 329 [M+H]<sup>+</sup>, RT 1.35 mins. <sup>1</sup>H NMR 300MHz (d<sub>6</sub>-DMSO) 8.32 (1H, s), 7.96 (1H, s), 7.30 (1H, s), 7.11 (1H, s), 7.74 (1H, s), 3.90 (3H, s), 2.95 (3H, s), 2.86-2.77 (4H, m), 1.93-1.68 (4H, m).

**Example 21.**

**7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1'H-spiro[pyrrolidine-3,2'-quinazolin]-4'(3'H)-one dihydrochloride salt**

Example 8 (0.20g), DCM (10ml) and HCl (2M in Et<sub>2</sub>O, 30ml) were stirred at room temperature for 1 hour. The reaction mixture was filtered and the solid dried *in vacuo* to yield the title compound as a solid (206mg, quantitative). TLC R<sub>f</sub> 0.13 (10% MeOH/DCM). LCMS 315 [M+H]<sup>+</sup>, RT 1.33 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.36 (1H, s), 8.25 (1H, s), 7.47 (1H, s), 6.61 (1H, s), 4.06 (3H, s), 3.77-3.65 (2H, m), 3.57 (2H, 2xd), 3.17 (3H, s), 2.90-2.70 (1H, m), 2.52-2.40 (1H, m).

Examples 21a – 22 were prepared in a similar manner to the method of Example 21:-

**Example 21a.**

**7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1'H-spiro[pyrrolidine-3,2'-quinazolin]-4'(3'H)-one hydrochloride**

From enantiomer 1 of Example 8 (60mg) and HCl (2M in Et<sub>2</sub>O, 20ml) to yield the title compound as a solid (50mg, 86%). TLC R<sub>f</sub> 0.10 (10% MeOH/DCM). LCMS 315 [M+H]<sup>+</sup>, RT 1.48 mins.

**Example 22.**

**7'-methoxy-6'-(1,3-oxazol-5-yl)-1'H-spiro[pyrrolidine-3,2'-quinazolin]-4'(3'H)-one hydrochloride**

From Example 9 (519mg) and HCl (2M in Et<sub>2</sub>O, 20ml) to yield the title compound as a solid (494 mg, quantitative yield). TLC R<sub>f</sub> 0.072 (10% MeOH/DCM). LCMS 301 [M+H]<sup>+</sup>, RT 1.36 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.48 (1H, s), 8.25 (1H, s), 7.52 (1H, s), 6.57 (1H, s), 4.06, (3H,s), 3.68 (2H, m), 3.55 (2H,m), 2.48 (2H, t).

**Example 23.**

**(3S)-Tetrahydrofuran-3-yl-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[piperidine-4,2'-quinazoline]-1-carboxylate**

A solution of Example 20 (50mg), (3S)-tetrahydrofuranylsuccinimidyl-carbonate (CAS 138499-08-8) (35mg) and TEA (0.021ml) in DCM (5ml) and DMF (5ml) were stirred at room temperature under nitrogen for 2 hours. The solvent was removed *in vacuo* and the reaction mixture was taken up in DCM (100ml) and washed with 1M HCl (40ml). The organic layer was separated, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica eluting with 0-5% MeOH/DCM to yield the title compound as a cream solid (36mg, 54%). TLC R<sub>f</sub> 0.43 (10% MeOH/DCM). LCMS 443 [M+H]<sup>+</sup>, RT 2.48 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.23 (1H, s), 8.22 (1H, s), 7.39 (1H, s), 6.66 (1H, s), 5.31-5.24 (1H, m), 4.24-4.12 (2H, m), 4.04 (3H, s), 4.01-3.84 (4H, m), 3.34-3.12 (2H, m), 3.14 (3H, s), 2.32-2.11 (6H,m).

Example 24 was prepared in a similar manner to the method of Example 23:-

**Example 24.****(3S)-Tetrahydrofuran-3-yl 7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxylate**

- 5 From Example 21 (50mg), (3S)-tetrahydrofuranylsuccinimidyl-carbonate (CAS 138499-08-8) (33mg) and TEA (0.1ml) in DCM (5ml) and DMF (10ml). Purification by column chromatography on silica eluting with 5-10% MeOH/DCM afforded the title compound as a beige solid (17mg, 28%). LCMS 429 [M+H]<sup>+</sup>, RT 2.39 mins. <sup>1</sup>H NMR 400MHz (d<sub>6</sub>-DMSO) 8.33 (1H, s), 8.00 (1H,s), 7.53 (1H, d), 7.32 (1H, s), 6.5 (1H, s), 5.12 (1H, m), 3.92 (3H, s), 3.8-3.42 (8H, m), 3.00 (3H, s), 2.09 (3H, m), 1.9 (1H, m).
- 10

**Example 25.****1-Benzoyl-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1'H-spiro[pyrrolidine-3,2'-quinazolin]-4'(3'H)-one**

- 15 To a stirred solution of benzoic acid (17.4mg), HBTU (54mg) and DIPEA (0.076ml) in DMF (10ml) was added, after 5 mins, Example 21 (50mg). The mixture was stirred under nitrogen for 2 hours. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in EtOAc (100ml) and washed with aqueous Na<sub>2</sub>CO<sub>3</sub> (30ml) and aqueous 1M HCl (30ml). The
- 20 organic layer was separated, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica eluting with 5-10% MeOH/DCM gradient to yield the title compound as a solid (32mg, 53%). TLC R<sub>f</sub> 0.13 (EtOAc). LCMS 419 [M+H]<sup>+</sup>, RT 2.57 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.27 and 8.26 (1H,2xs), 8.23 and 8.16 (1H, 2xs), 7.67-7.45 (5H, s), 7.43 and 7.40 (1H, 2xs), 6.59 and 6.53 (1H, 2xs), 4.05 and 4.00 (3H, 2xs), 4.05-3.67 (3H, m), 3.62 (1H,d), 3.25 and 3.21 (3H, 2xs), 2.95-2.65 (1H, m), 2.40-2.25 (1H, m).
- 25

Examples 26 - 42 were prepared in a similar manner to the method of

- 30 Example 25:-

**Example 26.****1-(3-Furoyl)-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1'H-spiro[pyrrolidine-3,2'-quinazolin]-4'(3H')-one**

From Example 21 (50mg) and 3-furoic acid (16mg) The residue was purified by trituration with MeOH:EtOAc:Et<sub>2</sub>O (1:3:10) to yield the title compound as a solid (24mg, 45%). TLC R<sub>f</sub> 0.49 (10% MeOH/DCM). LCMS 409 [M+H]<sup>+</sup>, RT 2.39 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.26 (1H, s), 8.25 (1H, s), 8.17 and 8.07 (1H, 2xs), 7.67 and 7.60 (1H, 2xs), 7.40 (1H, d), 6.89 and 6.79 (1H, 2xs), 6.53 (1H, d), 4.13-3.89 (7H, m), 3.23 (3H, s), 2.87-2.73 (1H, m), 2.45-2.38 (1H, m).

**Example 27.**

**7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1-(phenylacetyl)-1'H-spiro[pyrrolidine-3,2'-quinazolin]-4'(3'H)-one**

From Example 21 (50mg) and phenyl acetic acid (19mg) The residue was purified by trituration with MeOH:EtOAc:Et<sub>2</sub>O to yield the title compound as a solid (8mg, 13%). TLC R<sub>f</sub> 0.46 (5% MeOH/DCM). LCMS 433 [M+H]<sup>+</sup>, RT 2.65 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.36 and 8.32 (s), (1H, 2xs), 8.35 and 8.34 (1H, 2xs), 7.56-7.27 (6H, m), 6.62 and 6.43 (1H, 2xs), 4.15 and 4.12 (3H, 2xs), 4.03-3.76 (6H, m), 3.24 (3H, s), 2.92-2.79 (1H, m), 2.50-2.30 (1H, m).

**Example 28.**

**7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1-(tetrahydro-2H-pyran-4-ylcarbonyl)-1'H-spiro[pyrrolidine-3,2'-quinazolin]-4'(3'H)-one**

From Example 21 (50mg) and tetrahydropyran-4-carboxylic acid (19mg). The residue was purified by column chromatography on silica eluting with 4-7% MeOH/DCM to yield the title compound as a solid (35mg, 57%). TLC R<sub>f</sub> 0.46 (10% MeOH/DCM). LCMS 427 [M+H]<sup>+</sup>, RT 2.21 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.37-8.35 (2H, m), 7.52 (1H, s), 6.66 and 6.60 (1H, 2xs), 4.20-3.80 (7H, m), 3.70-3.50 (4H, m), 3.29 and 3.25 (3H, 2xs), 2.92-2.76 (2H, m), 2.50-2.31 (1H, m), 2.00-1.73 (4H, m).

**Example 29.**

**1-Isonicotinoyl-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1'H-spiro[pyrrolidine-3,2'-quinazolin]-4'(3'H)-one**

From Example 21 (50mg) and isonicotinic acid (18mg). The aqueous phases were re-extracted with DCM (3x50ml) after first basifying the acidic layer. The organic layers were combined, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica eluting

with 6-10% MeOH/DCM to yield the title compound as a solid (35mg, 58%).  
TLC R<sub>f</sub> 0.54 (10% MeOH/DCM). LCMS 420 [M+H]<sup>+</sup>, RT 1.91 mins. <sup>1</sup>H NMR  
300MHz (d<sub>4</sub>-MeOH) 8.89-8.86 and 8.78-8.76 (2H, 2xm), 8.39 and 8.37 (1H,  
2xs), 8.34 and 8.30 (1H, 2xs), 7.79-7.76 and 7.69-7.66 (2H, 2xm), 7.54 and  
5 7.51 (1H, 2xs), 6.67 and 6.65 (1H, 2xs), 4.17 and 4.14 (3H, 2xs), 4.17-3.66  
(4H, m), 3.36 and 3.32 (3H, 2xs), 3.00-2.78 (1H, m), 2.55-2.34 (1H, m).

**Example 30.**

**1-(3-Aminobenzoyl)-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1'H-  
spiro[pyrrolidine-3,2'-quinazolin]-4'(3'H)-one**

- 10 From Example 21 (100mg) and 3-aminobenzoic acid (35mg). Note: no acidic  
wash. The residue was purified using an MPLC Retrieve eluting with 0-5%  
MeOH/DCM followed by dissolving in DCM (30ml) and washing with dilute  
citric acid (20ml). The organic layer was separated, dried over MgSO<sub>4</sub>, filtered  
and concentrated *in vacuo* to yield the title compound as a solid (83mg, 72%).  
15 TLC R<sub>f</sub> 0.66 (10% MeOH/DCM). LCMS 434 [M+H]<sup>+</sup>, RT 2.02 mins. <sup>1</sup>H NMR  
300MHz (d<sub>6</sub>-DMSO) 8.36 and 8.34 (1H, 2xs), 8.04 and 7.96 (1H, 2xs), 7.67  
and 7.53 (1H, 2xs), 7.36 and 7.33 (1H, 2xs), 7.13-7.06 and 7.03-6.98 (1H,  
2xtr), 6.76-6.54 (3H, m), 6.52 (1H, s), 5.36-5.14 (2H, s, br), 3.96 and 3.93 (3H,  
2xs), 3.90-3.38 (4H, m), 3.33 (3H, s), 2.72-2.55 (1H, m), 2.22-2.03 (1H, m).

20 **Example 31.**

**7'-Methoxy-3'-methyl-1-(morpholin-4-ylacetyl)-6'-(1,3-oxazol-5-yl)-1'H-  
spiro[pyrrolidine-3,2'-quinazolin]-4'(3'H)-one**

- From Example 21 (50mg) and *N*-morpholino acetic acid (19mg). Note: no  
acidic wash. The residue was purified using an MPLC Retrieve eluting with 3-  
25 5% MeOH/DCM to yield the title compound as a solid (17mg, 30%). TLC R<sub>f</sub>  
0.43 (10% MeOH/DCM). LCMS 442 [M+H]<sup>+</sup>, RT 1.47 mins. <sup>1</sup>H NMR 300MHz  
(d<sub>6</sub>-DMSO) 8.34 (1H, s), 8.00 (1H, s), 7.49 and 7.45 (1H, 2xs), 7.33 (1H, s),  
6.51 and 6.44 (1H, 2xs), 3.91 (3H, s), 3.87-2.92 (10H, m), 3.00 and 2.98 (3H,  
2xs), 2.61-2.24 (5H, m), 2.17-1.97 (1H, m).

30 **Example 32.**

**tert-Butyl (3-{[7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-  
dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazolin]-1-  
yl]carbonyl}benzyl)carbamate**

From Example 21 (100mg) and Boc-(3-aminomethyl)-benzoic acid (65mg). The residue was purified using an MPLC Retrieve eluting with 0-5% MeOH/DCM to yield the title compound as a solid (115mg, 81%). TLC R<sub>f</sub> 0.66 (10% MeOH/DCM). LCMS 548 [M+H]<sup>+</sup>, RT 2.92 mins. <sup>1</sup>H NMR 300MHz (d<sub>6</sub>-DMSO) 8.34 and 8.30 (1H, 2xs), 8.01 and 7.92 (1H, 2xs), 7.66 and 7.52 (1H, 2xs), 7.48-7.20 (6H, m), 4.20-3.43 (9H, m), 3.00 (3H, s), 2.73-2.50 (1H, m), 2.17-2.00 (1H, m) 1.37 and 1.34 (9H, 2xs).

### Example 33.

#### 1-(2-Furoyl)-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1'H-spiro[pyrrolidine-3,2'-quinazolin]-4'(3'H)-one

From Example 21 (50mg) and 2-furoic acid (15mg). The residue was purified using an MPLC Retrieve eluting with 5% MeOH/DCM to yield the title compound as a solid (23mg, 43%). TLC R<sub>f</sub> 0.51 (10% MeOH/DCM). LCMS 409 [M+H]<sup>+</sup>, RT 2.37 mins. <sup>1</sup>H NMR 300MHz (d<sub>6</sub>-DMSO) 8.33 (1H, s), 8.01 (1H, s), 7.97 and 7.81 (1H, 2xs), 7.58 (1H, s), 7.33 (1H, s), 7.18-7.11 (1H, m), 6.70-6.59 (1H, m), 6.49 (1H, s), 4.10-3.97 (2H, m), 3.97 (3H, s), 3.83-3.68 (2H, m), 3.02 (3H, s), 2.71-2.53 (1H, m), 2.24-2.02 (1H, m).

### Example 33a.

#### 1-(2-Furoyl)-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1'H-spiro[pyrrolidine-3,2'-quinazolin]-4'(3'H)-one

From Example 21a (120mg) and 2-furoic acid (36mg). The residue was purified by column chromatography on silica eluting with 0-5% MeOH/DCM to yield the title compound as a solid (35mg, 26%). TLC R<sub>f</sub> 0.2 (5% MeOH/DCM). LCMS 409 [M+H]<sup>+</sup>, RT 2.42 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOD) 8.20 (2H, s), 7.80 (1H, s), 7.70 (1H, s), 7.40 (1H, s), 7.30-7.15 (1H, m), 6.75-6.55 (1H, m), 6.50 (1H, s), 4.30-4.15 (2H, m), 4.00-3.85 (5H, m), 3.20 (2H, s), 2.90-2.70 (1H, m), 2.45-2.25 (1H, m).

### Example 34.

#### 7'-Methoxy-3'-methyl-1-[(1-methyl-1H-pyrrol-2-yl)carbonyl]-6'-(1,3-oxazol-5-yl)-1'H-spiro[pyrrolidine-3,2'-quinazolin]-4'(3'H)-one

From Example 21 (50mg) and *N*-methylpyrrole-2-carboxylic acid (16mg). The residue was purified by preparative HPLC (Method A) to yield the title compound as a solid (7mg, 13%). LCMS 422 [M+H]<sup>+</sup>, RT 2.58 mins. <sup>1</sup>H NMR 300MHz (d<sub>6</sub>-DMSO) 8.32 (1H, s), 8.00 (1H, s), 7.55 (1H, s), 7.33 (1H, s),



6.94 (1H, s), 6.55 (1H, s, br), 6.50 (1H, s), 6.05 (1H, s, br), 3.95-3.85 (5H, m), 3.80-3.70 (5H, s), 3.07 (3H, s), 2.70-2.60 (1H, m), 2.20-2.10 (1H, m).

**Example 35.**

**7'-Methoxy-3'-methyl-1-[(1-methyl-1*H*-imidazol-2-yl)carbonyl]-6'-(1,3-oxazol-5-yl)-1'*H*-spiro[pyrrolidine-3,2'-quinazolin]-4'(3'*H*)-one**

From Example 21 (50mg) and 1-methyl-1*H*-imidazole-2-carboxylic acid (49mg) The residue was purified by column chromatography on silica eluting with 5%MeOH/DCM to yield the title compound as an off-white solid (35.9mg, 66%). TLC R<sub>f</sub> 0.08 (5% MeOH/DCM). LCMS 423 [M+H]<sup>+</sup>, RT 2.14 mins. <sup>1</sup>H NMR 300MHz (d<sub>6</sub>-DMSO) 8.30 (1H, s), 7.99 (1H, d), 7.52 and 7.32 (1H, 2xs), 7.28 (1H, s), 7.02 and 6.92 (1H, 2xs), 6.45 (1H, d), 4.25 (2H, m), 3.91 (3H, s), 3.88 (3H, s), 3.80-3.70 (2H, m), 3.00 (3H, s), 2.63-2.52 (1H, m), 2.18-2.04 (1H, m).

**Example 36.**

**1-(1-Benzothien-3-ylcarbonyl)-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1'*H*-spiro[pyrrolidine-3,2'-quinazolin]-4'(3'*H*)-one**

From Example 21 (50mg) and 1-benzothiophene-3-carboxylic acid (23mg). The residue was dissolved in DCM (10ml) and washed with water (3x10ml). The organic phase was separated, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to give a residue that was purified by column chromatography on silica eluting with 4%MeOH/DCM to yield the title compound as a solid (16mg, 26%). TLC R<sub>f</sub> 0.19 (5% MeOH/DCM). LCMS 475 [M+H]<sup>+</sup>, RT 2.97 mins. <sup>1</sup>H NMR 300MHz (d<sub>6</sub>-DMSO, 90°C) 8.21 (1H, s), 8.08-7.98 (4H, m), 7.45-7.40 (3H, m), 7.30 (1H, m), 6.54 (1H, s), 3.96 (3H, s), 3.95-3.71 (4H, m), 3.05 (3H, s), 2.72-2.63 (1H, m), 2.29-2.20 (1H, m).

**Example 37.**

**7'-methoxy-3'-methyl-1-(2-methyl-2-phenylpropanoyl)-6'-(1,3-oxazol-5-yl)-1'*H*-spiro[pyrrolidine-3,2'-quinazolin]-4'(3'*H*)-one**

From Example 21 (50mg) and α,α-dimethyl phenyl acetic acid (64mg). The residue was diluted with water (10ml) and extracted with EtOAc (3x10ml). The organic layers were combined, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by preparative HPLC (Method A) to yield the title compound as a solid (13.8mg, 23%). TLC R<sub>f</sub> 0.13

(5% MeOH/DCM). LCMS 461 [M+H]<sup>+</sup>, RT 2.95 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.16 (1H, s), 7.92 (1H, s), 7.34 (1H, s), 7.10-7.03 (4H, m), 6.90-6.83 (1H, m), 6.18 (1H, s), 3.99 (3H, s), 3.80-3.75 (2H, m), 3.32-3.22 (2H, m), 3.10 (3H, s), 3.80-3.70 (1H, m), 2.25-2.15 (1H, m), 1.70 (3H, s), 1.53 (3H, s).

5 **Example 38.**

**7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1-{5-[4-(trifluoromethyl)phenyl]-2-furoyl}-1'H-spiro[pyrrolidine-3,2'-quinazolin]-4'(3'H)-one**

From 5-[3-(trifluoromethyl) phenyl]-2-furoic acid (82mg), HBTU (121mg) and DIPEA (0.11ml) in DMF (20ml) and Example 21 (112mg). Purification by  
10 column chromatography on silica eluting with 3-5% MeOH/DCM afforded the title compound as a solid (110mg, 62%). TLC R<sub>f</sub> 0.28 (5%MeOH/DCM). LCMS 553 [M+H]<sup>+</sup>, RT 3.49 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.25 (1H, s), 8.22 (1H, s), 8.15 (1H, m), 8.02 and 7.9 (1H, s and d), 7.72-7.6 (2H, m), 7.4 and 7.29 (1H, s and d), 7.38 (1H, s), 7.21 and 7.10 (1H, d), 6.55 (1H, s), 4.4-  
15 3.9 (7H, m), 3.29 and 3.25 (3H, 2xs), 2.85 (1H, m), 2.40 (1H, m).

**Example 39.**

**N-[7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-1,3,3',4'-tetrahydro-1'H-spiro[indene-2,2'-quinazolin]-5-yl]acetamide**

From acetic acid (0.007ml), HBTU (49mg) and DIPEA (0.05ml) in DMF (5ml)  
20 and Example 13 (50mg). The residue was triturated in DCM/pentane to yield the title compound as a yellow solid (14.3 mg, 26%). TLC R<sub>f</sub> 0.32 (10%MeOH/DCM). LCMS 419 [M+H]<sup>+</sup>, RT 2.58 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.19 (1H, s), 8.18 (1H,s), 7.52 (1H, s), 7.22 (1H, s), 7.31 (1H, m), 7.18 (1H, d), 6.37 (1H, s), 3.95 (3H, s), 3.62 (2H, dd), 3.30 (2H, dd), 3.05 (3H, s),  
25 2.12 (3H, s).

**Example 40.**

**N-[7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-1,3,3',4'-tetrahydro-1'H-spiro[indene-2,2'-quinazolin]-5-yl]-3-furamide**

From 3-furoic acid (9mg), HBTU (30mg) and DIPEA (0.03ml) in DMF (3ml)  
30 and Example 13 (50mg) ). The residue was triturated in DCM/pentane to yield the title compound as a white solid (12.9 mg, 34%). TLC R<sub>f</sub> 0.51 (10%MeOH/DCM). LCMS 471 [M+H]<sup>+</sup>, RT 3.02 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.25 (1H, s), 8.23 (1H, s), 7.65 (1H, s), 7.50 (1H, dd), 7.39 (1H, s),

7.27 (1H, d), 6.97 (1H, dd), 6.43 (1H, s), 4.00 (3H, s), 3.70 (2H, dd), 3.35 (2H, dd), 3.10 (3H, s).

**Example 41.**

**N-(2,2-dimethylpropyl)-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1'H-spiro[cyclopentane-1,2'-quinazoline]-3-carboxamide**

From Example 18 (18mg), HBTU (38mg) and TEA (2 drops) in DMF (1ml) and neopentylamine (2 drops). Purification by preparative HPLC (Method A) afforded the title compound (5mg, 23%). LCMS: 427 [M+H]<sup>+</sup>, RT 2.92 mins. <sup>1</sup>H NMR 400MHz (d<sub>4</sub>-MeOH) 8.32 (1H, s), 8.17 (1H, s), 8.14 (1H, s), 7.91-7.86 (1H, tr), 7.30 (1H, s), 6.40 (1H, s), 3.97 (3H, s), 3.15 (3H, s), 3.04-2.90 (3H, m), 2.5-2.4 (1H, m), 2.23-2.20 (2H, d), 2.15-2.05 (1H, m), 2.00-1.88 (2H, m), 0.93 (9H, s).

**Example 42.**

**7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-3-(pyrrolidin-1-ylcarbonyl)-1'H-spiro[cyclopentane-1,2'-quinazolin]-4'(3'H)-one**

From Example 18 (73mg), HBTU (76mg) and TEA (0.055μl) in DMF (3ml) and pyrrolidine (0.034ml). Purification by preparative HPLC (Method A) afforded the title compound as a single diastereomer (18mg, 22%). LCMS: 411 [M+H]<sup>+</sup>, RT 2.50 mins. <sup>1</sup>H NMR 400MHz (d<sub>4</sub>-MeOH) 8.20 (1H, s), 8.17 (1H, s), 7.35 (1H, s), 6.45 (1H, s), 4.00 (3H, s), 3.60 (2H, m), 3.45 (2H, m), 3.27 (1H, m), 3.15 (3H, s), 2.40 (2H, m), 2.20 (2H, m), 1.95 (6H, m).

**Example 43.**

**1-[3-(Aminomethyl)benzoyl]-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1'H-spiro[pyrrolidine-3,2'-quinazolin]-4'(3'H)-one dihydrochloride**

Example 32 (53mg), DCM (3ml) and HCl (2M in Et<sub>2</sub>O, 10ml) were stirred at room temperature for 5 minutes. The reaction mixture was concentrated carefully *in vacuo* at 40°C to yield the title compound as a solid (58mg, quantitative). TLC R<sub>f</sub> 0.05 (10% MeOH/DCM). LCMS 448 [M+H]<sup>+</sup>, RT 1.57 mins. <sup>1</sup>H NMR 300MHz (d<sub>6</sub>-DMSO) 8.37 and 8.34 (1H, 2xs), 8.00 and 7.94 (1H, 2xs), 7.75-7.43 (5H, m), 7.36 and 7.31 (1H, 2xs), 6.57 and 6.50 (1H, 2xs), 4.10 and 4.04 (2H, 2xs), 3.95 and 3.90 (3H, 2xs), 3.95-3.50 (4H, m), 3.05 (3H, s), 2.76-2.58 (1H, m), 2.22-2.04 (1H, m).

**Example 44.**

**1-(2,2-Dimethylpropanoyl)-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1'H-spiro[pyrrolidine-3,2'-quinazolin]-4'(3'H)-one**

Intermediate 5 (100mg), DCM (10ml), DMF (2ml) and DIPEA (1ml) were stirred at room temperature under nitrogen for 5 mins. To the reaction mixture was added trimethyl acetyl chloride (0.03ml) and the mixture was stirred for 30 mins. The reaction was concentrated *in vacuo*, taken up in EtOAc (100ml) and washed with aqueous Na<sub>2</sub>CO<sub>3</sub> (30ml). The organic layer was separated, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica eluting with 4% MeOH /DCM to yield the title compound as a solid (4.6mg, 4.5%). TLC R<sub>f</sub> 0.56 (10% MeOH/DCM). LCMS 399 [M+H]<sup>+</sup>, RT 2.59 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.25 (2H, s), 8.40 (1H, s), 6.55 (1H, s), 4.03 (3H, s), 4.02-3.80 (4H, m), 3.21 (3H, s), 2.80-2.65 (1H, m), 2.29-2.21 (1H, m).

Examples 45-46 were prepared in a similar manner to the method of Example 44:-

**Example 45.**

**N-Ethyl-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxylic acid methylamide**

From Example 21 (100mg) and ethyl isocyanate (0.019ml). The residue was purified by trituration with MeOH:Et<sub>2</sub>O (1:20). The filtrate was concentrated *in vacuo* to yield the title compound as a solid (20mg, 20%). TLC R<sub>f</sub> 0.07 (5% MeOH/DCM). LCMS 386 [M+H]<sup>+</sup>, RT 2.12 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.35 (1H, s), 8.23 (1H, s), 7.43 (1H, s), 6.52 (1H, s), 4.00 (3H, s), 3.70-3.61 (4H, m), 3.33 (2H, q), 3.16 (3H, s), 2.76-2.64 (1H, m), 2.30-2.20 (1H, m), 1.13 (3H, tr).

**Example 46.**

**7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1-(piperidin-1-ylcarbonyl)-1'H-spiro[pyrrolidine-3,2'-quinazolin]-1-4'(3'H)-one**

From Example 21 (50mg) and 1-piperidinecarbonyl chloride (0.02ml). The residue was purified by trituration with MeOH to yield the title compound as an off-white solid (2.8mg, 5%). TLC R<sub>f</sub> 0.45 (10% MeOH/DCM). LCMS 426 [M+H]<sup>+</sup>, RT 2.70 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.21 (1H, s), 8.20 (1H, s), 7.38 (1H, s), 6.50 (1H, s), 4.01 (3H, s), 3.82-3.70 (2H, m), 3.64-3.50 (2H,

m), 3.37-3.20 (4H, m), 3.14 (3H, s), 2.69-2.57 (1H, m), 2.24-2.14 (1H, m), 1.69-1.52 (6H, m).

**Example 46a.**

**7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1-(piperidin-1-ylcarbonyl)-1'H-**

5 **spiro[pyrrolidine-3,2'-quinazolin]-4'(3'H)-one – Enantiomer 1**

Example 21a (40mg), 1-piperidinecarbonyl chloride (0.013ml), DCM (20ml) and DIPEA (0.037ml) were combined under a nitrogen atmosphere and stirred at room temperature for 1.5 hours. The mixture was taken up in EtOAc (100ml) and washed with 1M HCl (30ml) and saturated aqueous Na<sub>2</sub>CO<sub>3</sub> (30ml). The organic layer was separated, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The resulting residue was purified by column chromatography on silica eluting with 0-8% MeOH/DCM followed by preparative HPLC (Method A) to give the title compound as a solid (11mg, 25%).

15

Example 47 was prepared in a similar manner to the method of example 46a:-

**Example 47.**

**1-(Isopropyl)-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1'H-**

**spiro[pyrrolidine-3,2'-quinazolin]-4'(3'H)-one**

20 From Example 21 (50mg) and isopropyl sulfonyl chloride (0.027ml). The residue was purified by column chromatography on silica eluting with EtOAc and then 5-10% MeOH/DCM followed by trituration with EtOAc:Heptane (1:5) to yield the title compound as a solid (4.1 mg, 3.8%). TLC R<sub>f</sub> 0.56 (10% MeOH/DCM). LCMS 421 [M+H]<sup>+</sup>, RT 2.60 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.20 (1H, s), 8.19 (1H, s), 7.38 (1H, s), 6.50 (1H, s), 4.00 (3H, s), 3.78-3.54 (4H, m); 3.42-3.30 (1H, m), 3.19 (3H, s), 2.81-2.71 (1H, m), 2.34-2.22 (1H, m) 1.37 (3H, d), 1.34 (3H, d).

25

**Example 48.**

**iso-Propyl 7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-**

30 **1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxylate**

Intermediate 5 (100mg), dioxane (10ml), DMF (2ml), DIPEA (0.043ml) and isopropyl chloroformate (0.034ml) were combined and stirred at room temperature under a nitrogen atmosphere for 30 mins. The reaction mixture was diluted with EtOAc (100ml) and washed with aqueous Na<sub>2</sub>CO<sub>3</sub> (30ml).

The organic layer was separated, dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. The resulting residue was purified by trituration with EtOAc followed by column chromatography on silica eluting with EtOAc then 6-10% MeOH/DCM and trituration with EtOAc/heptane (1/8) twice to give the  
5 title compound (3mg, 3%). LCMS 401  $[\text{M}+\text{H}]^+$ , RT 2.78 mins.  $^1\text{H}$  NMR 300MHz ( $\text{d}_4\text{-MeOH}$ ) 8.20 (1H, s), 8.19 (1H, s), 7.4 (1H, s), 6.50 (1H, s), 4.95-4.8 (1H, m), 4.00 (3H, s), 3.75-3.55 (4H, m), 3.15 (3H, s), 2.75-2.55 (1H, m), 2.3-2.15 (1H, m) 1.35-1.20 (6H, m).

**Example 49.**

10 **Ethyl 7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxylate**

Intermediate 5 (100mg), ethyl chloroformate (0.028ml), DMF (10ml) and TEA (0.13ml) were combined and stirred at room temperature under a nitrogen atmosphere for 1 hour. The reaction mixture was concentrated *in vacuo* and  
15 the resulting residue purified by column chromatography on silica eluting with 0-10%MeOH/DCM. DMF had carried through this process and was removed by dissolving in DCM absorbing onto a solid phase cartridge, washing the DMF off with water followed by washing off the product with MeOH. The MeOH phase was concentrated *in vacuo* to afford the title compound as an  
20 off-white solid (8mg, 7%). TLC  $R_f$  0.40 (10% MeOH/DCM). LCMS 387  $[\text{M}+\text{H}]^+$ , RT 2.56 mins.  $^1\text{H}$  NMR 400MHz ( $\text{d}_6\text{-DMSO}$ ) 8.35 (1H, s), 8.00 (1H, s), 7.5 (1H, s, br), 7.3 (1H, s), 6.50 (1H, s), 4.15-4.0 (2H, m), 3.9 (3H, s), 3.6-3.4 (4H, m), 3.0 (3H, s), 2.1-2.0 (1H, m), 1.45-1.1 (4H, m).

**Example 50.**

25 **Phenyl 7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxylate**

Example 21 (50mg), phenyl chloroformate (0.018ml), DMF (10ml) and TEA (0.1ml) were combined and stirred at room temperature under a nitrogen atmosphere for 1 hour. The reaction mixture was concentrated *in vacuo* and  
30 the resulting residue purified by column chromatography on silica eluting with 0-10% MeOH/DCM. DMF had carried through this process and was removed by dissolving the residue in DCM, absorbing onto a solid phase cartridge, washing off the DMF with water followed by washing off the product with MeOH. The MeOH phase was evaporated *in vacuo* to afford the title

compound as a beige solid (6.5mg, 10%). LCMS 435 [M+H]<sup>+</sup>, RT 3.03 mins. <sup>1</sup>H NMR 400MHz (d<sub>6</sub>-DMSO) 8.35 (1H, s), 8.00 (1H, s), 7.65 (1H, d), 7.45-7.1 (5H, m), 6.55 (1H, d), 3.95 (3H, s), 3.9-3.5 (4H, m), 3.05 (3H, d), 2.7-2.5 (1H, m), 2.2-2.1 (1H, m).

5 **Example 51.**

**Benzyl 7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxylate**

Example 21 (50mg), benzyl chloroformate (0.02ml), DMF (5ml) and TEA (0.1ml) were combined and stirred at room temperature under a nitrogen  
10 atmosphere for 19 hours. The reaction mixture was concentrated *in vacuo* and the resulting residue purified by column chromatography on silica eluting with 0-10%MeOH/DCM to afford the title compound as a beige solid (43mg, 67%). TLC R<sub>f</sub> 0.275 (5% MeOH/DCM). LCMS 449 [M+H]<sup>+</sup>, RT 3.14 mins. <sup>1</sup>H NMR 400MHz (d<sub>6</sub>-DMSO) 8.35 (1H, s), 8.00 (1H, s), 7.55 (1H, d), 7.45-7.25  
15 (6H, m), 6.5 (1H, s), 5.15-5.0 (2H, m), 3.9 (3H, s), 3.8-3.45 (4H, m), 3.0 (3H, s), 2.6-2.45 (1H, m), 2.15-2.0 (1H, m).

**Example 52.**

**1-(3,3-Dimethyl-butyl)-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1'H-spiro[pyrrolidine-3,2'-quinazolin]-4'(3'H)-one**

20 Acetic acid (22mg) was added to a stirred solution of Example 21 (60mg), sodium triacetoxymethylborohydride (400mg) and 3,3-dimethyl butyraldehyde (34mg) in MeOH (5ml) at 0°C under nitrogen. The mixture was allowed to warm to room temperature and was heated to 52°C for 3 hours. The reaction mixture was concentrated *in vacuo* and the residue was triturated with  
25 MeOH:Et<sub>2</sub>O:Heptane. The filtrate was concentrated *in vacuo* and purified by preparative HPLC (Method A) to yield the title compound as a solid (26mg, 42%). TLC R<sub>f</sub> 0.63 (10% MeOH/DCM). LCMS 399 [M+H]<sup>+</sup>, RT 1.78 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.22 (1H, s), 8.17 (1H, s), 7.36 (1H, s), 6.45 (1H, s), 4.01 (3H, s), 3.14 (1H, d), 3.16 (3H, s), 2.90-2.80 (2H, m), 2.79 (1H, d),  
30 2.67-2.56 (2H, m), 2.55-2.50 (1H, m), 2.25-2.13 (1H, m), 1.53-1.46 (2H, m), 0.96 (9H, s).

**Example 53.**

**1-(3,3-Dimethyl-2-oxobutyl)-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1'H-spiro[pyrrolidine-3,2'-quinazolin]-4'(3'H)-one**

To a solution of Example 21 (75mg) and TEA (0.09ml) in THF (5ml) at 0°C, was added 1-bromopinacolone (0.04ml). The reaction mixture was stirred for 18 hours with slow warming to room temperature. The mixture was purified by column chromatography on silica eluting with 5%MeOH/DCM and the solid recovered was crystallised from MeOH/Et<sub>2</sub>O to yield the title compound as a solid (4.6mg, 6%). HPLC RT 1.75 mins. LCMS 413 [M+H]<sup>+</sup>, RT 1.76 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.22 (1H, s), 8.16 (1H, s), 7.45 (1H, s), 6.44 (1H, s), 6.74 (1H, s), 3.80-3.57 (2H, dd), 3.18 (3H, s), 3.16-3.10 (1H, d), 2.96-2.88 (1H, m), 2.82-2.76 (1H, d), 2.72-2.65 (1H, m), 2.52-2.42 (1H, m), 2.23-2.12 (1H, m), 1.18 (9H, s).

#### Example 54.

#### 2-[7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazolin]-1-yl]-N,N-dimethylacetamide

To a solution of Example 21 (50mg) and TEA (0.06ml) in THF (5ml) at 0°C, was added 2-chloro-N,N-dimethylacetamide (0.01ml). The reaction mixture was stirred for 18 hours with slow warming to room temperature. 2-chloro-N,N-dimethylacetamide (0.01ml) was added and the reaction mixture stirred at room temperature overnight. The mixture was concentrated *in vacuo* and purified by column chromatography on silica eluting with 5-10%MeOH/DCM to yield the title compound as a solid (20mg, 39%). TLC R<sub>f</sub> 0.38 (10% MeOH/DCM). LCMS 400 [M+H]<sup>+</sup>, RT 1.41 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.18 (1H, s), 8.17 (1H, s), 7.44 (1H, s), 6.44 (1H, s), 3.96 (3H, s), 3.55-3.35 (2H, dd), 3.28-3.20 (2H, m), 3.15 (3H, s), 3.10 (3H, s), 3.95 (3H, s), 2.90-2.70 (2H, m), 2.50-2.40 (1H, m), 2.23-2.12 (1H, m).

#### Example 55.

#### Cyclohexyl 7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxylate

To a solution of Example 21 (50mg) and TEA (0.1ml) in DCM (5ml) at room temperature, was added carbonic acid cyclohexylester 2,5-dioxo-pyrrolidin-1-yl ester (43mg) and the mixture stirred for 18 hours at room temperature. The reaction mixture was concentrated *in vacuo* and purified by preparative HPLC (Method A) to yield the title compound as a solid (7.7mg, 12%). LCMS 441 [M+H]<sup>+</sup>, RT 3.31 mins. <sup>1</sup>H NMR 400MHz (d<sub>4</sub>-MeOH) 8.15



(2H, 2xs), 7.32 (1H, s), 6.44 (1H, s), 4.65-4.55 (1H, m), 3.90 (3H, s), 3.68-3.56 (4H, m) 3.07 (3H, s), 2.60-2.54 (1H, m), 2.22-2.12 (1H, m), 1.90-1.15 (5H, m).

Examples 56-58 were prepared in a similar manner to the method of example 55:-

**Example 56.**

**7'-Methoxy-3'-methyl-1-(morpholin-4-ylcarbonyl)-6'-(1,3-oxazol-5-yl)-1'H-spiro[pyrrolidine-3,2'-quinazolin]-4'(3'H)-one**

From Example 21 (50mg) and 4-morpholine carbonyl chloride (0.02ml). The residue was purified by column chromatography on silica eluting with 3-5%MeOH/DCM to yield the title compound as a solid (20.6 mg, 37%). TLC R<sub>f</sub> 0.44 (10% MeOH/DCM). LCMS 428 [M+H]<sup>+</sup>, RT 2.22 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.18 (1H, s), 8.14 (1H, s), 7.32 (1H, s), 6.45 (1H, s), 3.96 (3H, s), 3.80-3.70 (2H, m), 3.68-3.60 (4H, m), 3.60-3.53 (2H, m), 3.35-3.20 (4H, m), 3.10 (3H, s) 2.65-2.55 (1H, m), 2.22-2.12 (1H, m).

**Example 57.**

**(3R)-Tetrahydrofuran-3-yl (3-{[7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazolin]-1-yl]carbonyl}benzyl)carbamate**

From Example 43 (50mg) and carbonic acid 2,5-dioxo-pyrrolidin-1-yl ester tetrahydro-furan-3-(S)-yl ester (26mg). The residue was diluted with DCM (50ml), washed with 1M HCl (30ml) and washed with aqueous Na<sub>2</sub>CO<sub>3</sub> solution (30ml). The organic layer was separated, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by preparative HPLC (Method A) to yield the title compound as a solid (26mg, 41%). TLC R<sub>f</sub> 0.53 (10% MeOH/DCM). LCMS 561 [M+H]<sup>+</sup>, RT 2.42 mins. <sup>1</sup>H NMR 300MHz (d<sub>6</sub>-DMSO) 8.30 (1H, d), 8.00 and 7.90 (1H, 2xs), 7.85 and 7.75 (1H, 2xm), 7.65 and 7.53 (1H, 2xs) 7.45-7.22 (5H, m), 6.46 (1H, s), 5.10-5.00 (1H, m) 4.22-4.15 (1H, m), 4.14-4.06 (1H, m), 3.90 (3H, m) 3.75-3.60 (8H, m), 3.00 (3H, m), 2.70-2.55 (1H, m), 2.18-2.00 (2H, m), 2.00-1.75 (1H, m).

**Example 58.**

**1-(tert-Butoxycarbonyl)piperidin-4-yl 7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxylate**

From Example 21 (73mg) and 4-(2,5-dioxo-pyrrolidin-1-yloxy-carbonyloxy)-piperidine-1-carboxylic acid *tert*-butyl ester (71mg). The residue was purified by column chromatography on silica eluting with 5% MeOH/DCM to yield the title compound as a solid (93 mg, 83%). TLC R<sub>f</sub> 0.23 (5% MeOH/DCM).

- 5 LCMS 542 [M+H]<sup>+</sup>, RT 3.08 mins. <sup>1</sup>H NMR 400MHz (d<sub>4</sub>-MeOH) 8.15 (2H, 2xs), 7.40 (1H, s), 6.45 (1H, s), 4.85-4.80 (1H, m), 3.95 (3H, s), 3.80-3.69 (6H, m), 3.11 (3H, s), 3.10-2.97 (2H, m) 2.70-2.60 (1H, m), 2.20-2.10 (1H, m), 1.90-1.80 (3H, m) 1.70-1.60 (1H, m), 1.40 (9H, s).

**Example 59.**

- 10 **Piperidin-4-yl 7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxylate**

- To a solution of Example 58 (73mg) in DCM (3ml) was added 1M HCl in Et<sub>2</sub>O (3ml) and the mixture stirred at room temperature for 30mins. The precipitate formed was partitioned between 2M NaOH (20ml) and DCM (20ml). The  
15 organic layer was separated, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to yield the title compound as a clear glass (35.5mg, 60%). LCMS 442 [M+H]<sup>+</sup>, RT 1.55 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.20 (1H, s), 8.15 (1H, s), 7.32 (1H, s), 6.45 (1H, s), 4.80-4.75 (1H, m), 3.95 (3H, s), 3.85-3.60 (4H, m), 3.10 (3H, s), 3.08-2.90 (2H, m) 2.75-2.55 (3H, m), 2.25-2.15 (1H, m),  
20 2.00-1.75 (2H, m) 1.68-1.30 (2H, m).

**Example 60.**

**1-Acetyl piperidin-4-yl 7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxylate**

- To a stirred solution of acetic acid (1 drop), HBTU (17mg) and TEA (2 drops)  
25 in DMF (2ml) was added after 5 mins Example 59 (19.5mg). The mixture was stirred for 3 hours then concentrated *in vacuo*. The residue was purified by preparative HPLC (Method A) to yield the title compound as a solid (8.8mg, 41%). LCMS 484 [M+H]<sup>+</sup>, RT 2.31 mins. <sup>1</sup>H NMR 400MHz (d<sub>4</sub>-MeOH) 8.15 (1H, s), 8.12 (1H, s), 7.31 (1H, s), 6.45 (1H, s), 4.95-4.85 (1H, m), 3.97 (3H, s), 3.80-3.60 (6H, m), 3.50-3.32 (2H, m) 3.10 (3H, s), 2.70-2.60 (4H, m) 2.25-2.13 (1H, m), 2.10-2.00 (2H, m), 1.98-1.80 (2H, m).  
30

**Example 61.**

**(3S)-Tetrahydrofuran-3-yl (3-([7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazolin]-1-yl]carbonyl)ethyl)carbamate**

To a stirred solution of *N*-*tert*-butoxycarbonyl-beta-alanine (54mg) in DMF (5ml), at room temperature under nitrogen was added HBTU (108mg) and DIPEA (0.15ml). Example 21 (100mg), was added and the reaction stirred for 18 hours. The reaction mixture was concentrated *in vacuo*, dissolved in 1% MeOH/EtOAc (50ml) and washed with aqueous Na<sub>2</sub>CO<sub>3</sub> solution (10ml) and 1M HCl solution (10ml). The organic layer was separated, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to give a brown oil. Purification by column chromatography on silica eluting with 3% MeOH/DCM afforded a brown solid. This was dissolved in a solution of 1M HCl in Et<sub>2</sub>O (5ml) and the mixture stirred at room temperature for 1 hour. The reaction mixture was concentrated *in vacuo* to yield a brown oil which was dissolved in THF/H<sub>2</sub>O (2.5ml/2.5ml). To this was added NaHCO<sub>3</sub> (35mg) and carbonic acid 2,5-dioxo-pyrrolidin-1-yl ester tetrahydro-furan-3(S)-yl ester (40mg). After stirring for 16 hours at room temperature, the THF was removed *in vacuo* and the aqueous residue partitioned between water (10ml) and 10%MeOH/DCM (10ml). The organic layer was separated, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to give a brown oil. Purification by column chromatography on silica eluting with 5-10%MeOH/DCM afforded the title compound as a brown solid 65mg (48%). TLC R<sub>f</sub> 0.12 (5% MeOH/DCM). LCMS 500 [M+H]<sup>+</sup>, RT 2.16 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.20 (2H, 2xs), 7.34 (1H, s), 6.45 (1H, d), 5.22-5.10 (1H, m), 3.95 (3H, s), 3.90-3.60 (8H, m), 3.45-3.35 (2H, m) 3.13 (3H, d), 2.75-2.52 (2H, m) 2.50-2.42 (1H, m), 2.32-1.90 (3H, m).

**Example 62.**

**7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-N-phenyl-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

To a solution of aniline (0.02ml) in dry DCM (15ml) under nitrogen cooled to -78°C was added triphosgene (19mg) followed by TEA (0.05ml). The mixture was allowed to warm to 0°C and stirred for 30mins. Addition of Example 21 (70mg) then took place along with more TEA (0.05ml). The reaction mixture

was allowed to warm to room temperature and stirred overnight. The reaction mixture was diluted with DCM (15ml) and successively washed with 1M aqueous HCl (2x15ml), H<sub>2</sub>O (15ml), NaHCO<sub>3</sub> solution (2x15ml) and brine (15ml). The organic layer was separated, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica eluting with EtOAc then 10% MeOH/DCM followed by trituration in MeOH/pentane to afford the title compound as a white solid (7.4mg, 9%). TLC R<sub>f</sub> 0.44 (10% MeOH/DCM). LCMS 434 [M+H]<sup>+</sup>, RT 2.74 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.23 (1H, s), 8.14 (1H, s), 7.31-7.25 (2H, tr), 7.28-7.23 (2H, tr), 7.04-6.99 (1H, tr), 6.50 (1H, s), 3.97 (3H, s), 3.83-3.70 (4H, m), 3.16 (3H, s), 2.77-2.63 (1H, m), 2.34-2.24 (1H, m).

Examples 63-83 were prepared in a similar manner to the method of example 62:-

**Example 63.**

**7'-methoxy-N,3'-dimethyl-6'-(1,3-oxazol-5-yl)-4'-oxo-N-phenyl-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

From Example 21 (70mg) and N-methylaniline (0.02ml). Purification by trituration in EtOAc/pentane afforded the title compound as a green solid (26mg, 32%). TLC R<sub>f</sub> 0.15 (EtOAc). LCMS 448 [M+H]<sup>+</sup>, RT 2.87 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.20 (1H, s), 8.11 (1H, s), 7.40-7.33 (3H, m), 7.20-7.15 (3H, m), 6.43 (1H, s), 3.98 (3H, s), 3.52-3.23 (4H, m), 3.19 (3H, s), 2.94 (3H, s), 2.53-2.41 (1H, m), 2.09-1.98 (1H, m).

**Example 64.**

**1-([4-(4-Chlorophenoxy)piperidin-1-yl]carbonyl)-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1'H-spiro[pyrrolidine-3,2'-quinazolin]-4'(3'H)-one**

From Example 21 (50mg) and 4-(4-chlorophenoxy)-piperidine (32mg). Purification by column chromatography on silica eluting with 5-10% MeOH/DCM followed by trituration in DCM/pentane afforded the title compound as a yellow solid (15mg, 21%). TLC R<sub>f</sub> 0.47 (10%MeOH/DCM). LCMS 554 [M+H]<sup>+</sup>, RT 3.54 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.23 (1H, s), 7.40 (1H, s), 7.30-7.26 (2H, d), 7.07-6.94 (2H, d), 6.52 (1H, s), 4.60-4.50 (1H, m), 4.02 (3H, s), 3.84-3.77 (2H, m), 3.67-3.53 (4H, m), 3.17 (3H, s), 2.73-2.59 (1H, m), 2.26-2.16 (1H, m), 2.17-1.83 (1H, m), 1.82-1.64 (1H, m).

**Example 65.****N-Benzyl-7'-methoxy-N,3'-dimethyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

From Example 21 (50mg) and N-benzylmethylamine (0.017ml). Purification by  
5 column chromatography on silica eluting with 5% MeOH/DCM followed by  
trituration in DCM/pentane afforded the title compound as an off-white solid  
(31mg, 52%). TLC R<sub>f</sub> 0.52 (10%MeOH/DCM). LCMS 462 [M+H]<sup>+</sup>, RT 2.94  
mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.18 (1H, s), 8.14 (1H, s), 7.36 (1H, s),  
7.25-7.21 (2H, d), 6.47 (1H, s), 4.52-4.47 (1H, d), 4.35-4.30 (1H, d), 3.95 (3H,  
10 s), 3.97-3.77 (1H, m), 3.68-3.52 (4H, m), 3.10 (3H, s), 2.77 (3H, s), 2.67-2.56  
(1H, m), 2.20-2.10 (1H, m).

**Example 66.****N,N-Diethyl-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

15 From Example 21 (100mg) 4-piperidone monohydrate hydrochloride (40mg)  
and TEA (0.17ml). Purification by column chromatography on silica eluting  
with 5% MeOH/DCM followed by trituration in DCM/pentane afforded the title  
compound as a magnolia solid (58mg, 54%). TLC R<sub>f</sub> 0.47 (10%MeOH/DCM).  
LCMS 414 [M+H]<sup>+</sup>, RT 2.67 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.17 (2H,  
20 2xs), 7.35 (1H, s), 6.47 (1H, s), 3.98 (3H, s), 3.79-3.71 (2H, m), 3.60-3.50  
(2H, m), 3.30-3.21 (4H, m), 3.13 (3H, s), 2.69-2.56 (1H, m), 2.21-2.11 (1H,  
m), 1.15-1.10 (1H, tr).

**Example 67.****7'-Methoxy-3'-methyl-1-[(4-methylpiperazin-1-yl)carbonyl]-6'-(1,3-oxazol-5-yl)-1'H-spiro[pyrrolidine-3,2'-quinazolin]-4'(3'H)-one**

25 From Example 21 (100mg) and methylpiperazine (0.01ml). The product in  
DCM (15ml) was extracted with 1M HCL (2x15ml), the aqueous layers were  
combined, basified with solid NaOH and extracted with DCM (3x20ml). The  
organic layers were combined, dried over MgSO<sub>4</sub>, filtered and concentrated *in  
vacuo*. The residue was triturated in DCM/pentane and further purified by  
30 preparative HPLC (Method A) to afford the title compound as a yellow solid  
(5.6mg, 10%). TLC R<sub>f</sub> 0.08 (10%MeOH/DCM). LCMS 441 [M+H]<sup>+</sup>, RT 1.48  
mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.19 (2H, 2xs), 7.36 (1H, s), 6.48 (1H, s),

3.97 (3H, s), 3.79-3.74 (2H, m), 3.63-3.52 (2H, m), 3.40-3.28 (4H, m), 3.13 (3H, s), 2.66-2.58 (1H, m), 2.46-2.40 (4H, m), 2.29 (3H, s), 2.22-2.13 (1H, m).

**Example 68.**

**N-(2,4-Difluorophenyl)-7'-methoxy-N,3'-dimethyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

From Example 21 (100mg) and 2,4-difluoro-N-methylaniline (18.6mg). Purification by trituration in DCM/pentane afforded the title compound as a white solid (26mg, 41%). TLC R<sub>f</sub> 0.47 (10% MeOH/DCM). LCMS 484 [M+H]<sup>+</sup>, RT 2.93 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.17 (1H, s), 8.11 (1H, s), 7.36-7.27 (1H, m), 7.34 (1H, s), 7.10-6.93 (2H, m), 6.40 (1H, s), 3.96 (3H, s), 3.50-3.40 (1H, m), 3.36-3.24 (3H, m), 3.10 (3H, s), 2.96 (3H, s), 2.56-2.45 (1H, m), 2.09-2.00 (1H, m).

**Example 69.**

**tert-Butyl 4-[(7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazolin]-1-yl)carbonyl]piperazine-1-carboxylate**

From Example 21 (100mg) and t-butyl-1-piperazine (48.4mg). Purification by column chromatography on silica eluting with 5% MeOH/DCM and trituration with DCM/pentane yielded the title compound as a yellow solid (34.5mg, 25%). TLC R<sub>f</sub> 0.59 (10% MeOH/DCM). LCMS 527 [M+H]<sup>+</sup>, RT 3.01 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.3 (2H, 2xs), 7.40 (1H, s), 6.50 (1H, s), 4.05 (3H, s), 3.85-3.75 (2H, m), 3.80-3.65 (2H, m), 3.50-3.40 (4H, m), 3.40-3.25 (4H, m), 3.15 (3H, s), 2.70-2.60 (1H, m), 2.25-2.15 (1H, m), 1.45 (9H, s).

**Example 70.**

**N-(2-Chlorophenyl)-7'-methoxy-N,3'-dimethyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

From Example 21 (50mg) and 2-chloro-N-methylaniline (18.2mg). The residue was purified by column chromatography on silica eluting with 5% MeOH/DCM to yield the title compound as a solid (11mg, 18%). TLC R<sub>f</sub> 0.23 (5% MeOH/DCM). LCMS 482 [M+H]<sup>+</sup>, RT 2.95 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.20 (1H, s), 8.10 (1H, s), 7.50-7.20 (5H, m), 6.45 (1H, s), 4.00 (3H, s), 3.50-3.40 (1H, m), 3.35-3.10 (3H, m), 3.10 (3H, s), 2.95 (3H, s), 2.55-2.40 (1H, m), 2.10-2.00 (1H, m).

**Example 71.****7'-Ethoxy-N,3'-dimethyl-6'-(1,3-oxazol-5-yl)-4'-oxo-N-[2-(trifluoromethoxy)phenyl]-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

- 5 From Example 21 (50mg) and 2-trifluoromethoxy-N-methylaniline (24.9mg). The precipitate was collected and dried to yield the title compound as a light brown solid (32.3mg, 47%). TLC R<sub>f</sub> 0.31 (10% MeOH/DCM). LCMS 532 [M+H]<sup>+</sup>, RT 3.16 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.20 (1H, s), 8.10 (1H, s), 7.45-7.30 (5H, m), 6.40 (1H, s), 3.95 (3H, s), 3.55-3.45 (1H, m), 3.40-3.25 (2H, m), 3.20-  
10 3.10 (4H, m), 2.95 (3H, s), 2.55-2.45 (1H, m), 2.10-2.00 (1H, m).

**Example 72.****1-[[4-(2-Fluorophenyl)piperidin-1-yl]carbonyl]-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1'H-spiro[pyrrolidine-3,2'-quinazolin]-4'(3'H)-one**

- From Example 21 (50mg) and 4-(2-fluorophenyl)piperidine (23mg). The residue  
15 was purified by column chromatography on silica eluting with 5% MeOH/DCM to yield the title compound as a white solid (29mg, 43%). LCMS 520 [M+H]<sup>+</sup>, RT 3.31 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.25 (2H, s), 7.40 (1H, s), 7.25-7.15 (2H, m), 7.10-7.00 (2H, m), 6.55 (1H, s), 4.00 (3H, s), 4.00-3.75 (4H, m), 3.65-3.55 (2H, m), 3.15 (3H, s), 3.15-2.85 (3H, m), 2.70-2.60 (1H, m), 2.25-2.15 (1H,  
20 m), 1.85-1.60 (4H, m).

**Example 73.****7'-Methoxy-N,3'-dimethyl-6'-(1,3-oxazol-5-yl)-4'-oxo-N-[2-(trifluoromethyl)phenyl]-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

- 25 From Example 21 (50mg) and 2-(methylamino) benzotrifluoride (23mg). The residue was purified by column chromatography on silica eluting with 5% MeOH/DCM to yield the title compound as a solid (8.5mg, 13%). TLC R<sub>f</sub> 0.18 (5% MeOH/DCM). LCMS 516 [M+H]<sup>+</sup>, RT 3.01 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.20 (1H, s), 8.10 (1H, s), 7.75-7.60 (2H, m), 7.35-7.50 (3H, m), 6.40 (1H,  
30 s), 3.95 (3H, s), 3.80-3.35 (2H, m), 3.25-3.10 (5H, m), 2.95 (3H, s), 2.55-2.35 (1H, m), 2.10-2.00 (1H, m).

**Example 74.**

**Methyl 4-[[7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazolin]-1-yl]carbonyl](methylamino)benzoate**

From Example 21 (500mg) and methyl-4-(methylamino)benzoate (215mg).

- 5 Trituration with DCM/pentane afforded the title compound as a yellow solid (484mg, 74%). TLC R<sub>f</sub> 0.53 (10% MeOH/DCM). LCMS 506 [M+H]<sup>+</sup>, RT 2.78 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.20 (1H, s), 8.10 (1H, s), 7.95 (2H, d), 7.45 (1H, s), 7.35 (2H, d), 6.45 (1H, s), 4.05 (3H, s), 3.85 (3H, s), 3.60-3.50 (2H, m), 3.25 (3H, s), 3.00 (3H, s), 2.65-2.55 (1H, m), 2.15-2.05 (1H, m).

10 **Example 75.**

**7'-Methoxy-N-(4-methoxyphenyl)-N,3'-dimethyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

- From Example 21 (50mg) and N-methyl-p-anisidine (18mg). The residue was purified by column chromatography on silica eluting with 5% MeOH/DCM to yield the title compound as a pale green solid (15mg, 24%). TLC R<sub>f</sub> 0.44 (10% MeOH/DCM). LCMS 478 [M+H]<sup>+</sup>, RT 2.79 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.20 (1H, s), 8.10 (1H, s), 7.35 (1H, s), 7.10 (2H, d), 6.85 (2H, d), 6.40 (1H, s), 4.00 (3H, s), 3.70 (3H, s), 3.55-3.35 (2H, m), 3.20 (2H, m), 3.10 (3H, s), 2.95 (3H, s), 2.50-2.40 (1H, m), 2.05-1.95 (1H, m).

20 **Example 76.**

**7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1-[[4-(pyridin-4-yloxy)piperidin-1-yl]carbonyl]-1'H-spiro[pyrrolidine-3,2'-quinazolin]-4'(3'H)-one**

- From Example 21 (50mg) and 4-(piperidin-4-yloxy)-pyridine (CAS 224178-65-8) (46mg). The residue was purified by column chromatography on silica eluting with 7% MeOH/DCM, followed by preparative HPLC (Method B) to yield the title compound as a solid (10mg, 15%). LCMS 519 [M+H]<sup>+</sup>, RT 1.64 mins. <sup>1</sup>H NMR 400MHz (d<sub>4</sub>-MeOH) 8.35 (2H, 2xs), 8.20 (1H, s), 8.18 (1H, s), 7.35 (1H, s), 7.10 (1H, s), 7.05 (1H, s), 6.50 (1H, s), 4.75 (1H, m), 3.95 (3H, s), 3.80-3.75 (2H, m), 3.60-3.50 (4H, m), 3.30-3.20 (2H, m), 3.15 (3H, s), 2.65-2.55 (1H, m), 2.20-2.10 (1H, m), 2.05-1.95 (2H, m), 1.80-1.65 (2H, m).

30 **Example 77.**

**1-[[4-(1-Benzofuran-2-yl)piperidin-1-yl]carbonyl]-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1'H-spiro[pyrrolidine-3,2'-quinazolin]-4'(3'H)-one**



From Example 21 (50mg) and 4-(2-benzofuranyl)-piperidine (CAS 54477-05-3) (26mg). The residue was purified by column chromatography on silica eluting with 30-100% EtOAc/heptane followed by 5% MeOH/DCM. Trituration in DCM/pentane afforded the title compound as a yellow solid (4mg, 6%).

5 TLC R<sub>f</sub> 0.44 (EtOAc). LCMS 5427 [M+H]<sup>+</sup>, RT 3.53 mins. <sup>1</sup>H NMR 400MHz (d<sub>4</sub>-MeOH) 8.15 (1H, s), 7.45 (1H, d), 7.35 (2H, m), 7.20-7.10 (2H, m), 6.50 (1H, s), 6.45 (1H, s), 3.95 (3H, s), 3.90-3.55 (4H, m), 3.65-3.55 (2H, m), 3.15 (3H, s), 3.05-2.95 (3H, m), 2.65-2.55 (1H, m), 2.25-2.15 (1H, m), 2.15-2.05 (2H, m), 1.75-1.60 (2H, m).

10 **Example 78.**

**7'-Methoxy-N,3'-dimethyl-6'-(1,3-oxazol-5-yl)-4'-oxo-N-pyridin-2-yl-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

From Example 21 (50mg) and 2-(methylamino)pyridine (0.013ml). The residue was purified by column chromatography on silica eluting with 4% MeOH/DCM to yield the title compound as a solid (9.2mg, 16%). LCMS 449 [M+H]<sup>+</sup>, RT 2.33 mins. <sup>1</sup>H NMR 400MHz (d<sub>4</sub>-MeOH) 8.30 (1H, d), 8.15 (1H, s), 8.10 (1H, s), 7.75 (1H, t), 7.30 (1H, s), 7.15 (1H, d), 7.05 (1H, t), 6.45 (1H, s), 3.95 (3H, s), 3.65-3.35 (4H, m), 3.25 (3H, s), 3.05 (3H, s), 2.60-2.50 (1H, m), 2.15-2.05 (1H, m).

20 **Example 79.**

**N-(2-Cyanoethyl)-7'-methoxy-N,3'-dimethyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

From Example 21 (50mg) and N-methyl-β-alanine nitrile (0.01ml). The residue was purified by column chromatography on silica eluting with 5% MeOH/DCM to yield the title compound as a yellow solid (30mg, 50%). TLC R<sub>f</sub> 0.46 (10% MeOH/DCM). LCMS 425 [M+H]<sup>+</sup>, RT 2.28 mins. <sup>1</sup>H NMR 400MHz (d<sub>4</sub>-MeOH) 8.20 (2H, 2xs), 7.35 (1H, s), 6.50 (1H, s), 3.95 (3H, s), 3.80-3.70 (2H, m), 3.60-3.50 (3H, m), 3.45-3.35 (1H, m), 3.10 (3H, s), 3.00 (3H, s), 2.75-2.70 (2H, t), 2.65-2.60 (1H, m), 2.20-2.10 (1H, m).

30 **Example 80.**

**N-Ethyl-N-isopropyl-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

From Example 21 (70mg) and *N*-ethylisopropylamine (34mg). The residue was purified by column chromatography on silica eluting with 3% MeOH/DCM followed by dissolving in DCM (50ml) and washing with aqueous 10% Na<sub>2</sub>CO<sub>3</sub> (20ml), 1M HCl (aq) (20ml) and water (20ml). The organic layer was separated, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to yield the  
5 title compound as a solid (8.5mg, 11%). LCMS 428 [M+H]<sup>+</sup>, RT 2.81 mins. <sup>1</sup>H NMR 400MHz (d<sub>4</sub>-MeOH) 8.20 (2H, 2xs), 7.35 (1H, s), 6.45 (1H, s), 4.00 (3H, s), 3.95-3.85 (1H, m), 3.80-3.70 (2H, m), 3.60-3.50 (2H, m), 3.25-3.15 (1H, m), 3.10 (3H, s), 3.10-3.00 (1H, m), 2.65-2.55 (1H, m), 2.20-2.10 (1H, m),  
10 1.20-1.10 (6H, m), 1.05-1.00 (3H, t).

#### Example 80a.

#### *N*-Ethyl-*N*-isopropyl-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1*H*,1'*H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide

From Example 21a (70mg) and *N*-ethylisopropylamine (34mg). The residue was purified by preparative HPLC (method A) to yield the title compound as a  
15 solid (2.5mg, 3.3%). LCMS 428 [M+H]<sup>+</sup>, RT 2.79 mins. <sup>1</sup>H NMR 400MHz (d<sub>4</sub>-MeOD) 8.20 (1H, s), 8.15 (1H, s), 7.35 (1H, s), 6.50 (1H, s), 4.00 (3H, s), 3.85-3.95 (1H, m), 3.65-3.75 (2H, m), 3.45-3.55 (2H, m), 3.25-3.15 (1H, m), 3.15-3.00 (1H, m), 3.10 (3H, s), 2.65-2.55 (1H, m), 2.20-2.10 (1H, m), 1.15-  
20 1.10 (6H, m), 1.05 (3H, t).

#### Example 81.

#### 7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-*N*-(2,2,2-trifluoroethyl)-3',4'-dihydro-1*H*,1'*H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide

From Example 21 (50mg) and 2,2,2-trifluoroethylamine (19mg). The residue was purified by column chromatography on silica eluting with 5-10% MeOH/DCM to yield the title compound as an off-white solid (7.5mg, 13%).  
25 TLC R<sub>f</sub> 0.21 (10% MeOH/DCM). LCMS 440 [M+H]<sup>+</sup>, RT 2.46 mins. <sup>1</sup>H NMR 400MHz (d<sub>4</sub>-MeOH) 8.20 (2H, 2xs), 7.35 (1H, s), 6.50 (1H, s), 3.95 (3H, s), 3.85 (2H, q), 3.65 (4H, m), 3.10 (3H, s), 2.75-2.65 (1H, m), 2.25-2.15 (1H, s).

#### Example 82.

#### 7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-*N*-pyrimidin-2-yl-3',4'-dihydro-1*H*,1'*H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide

From Example 21 (50mg) and 2-aminopyrimidine (13mg). The residue was purified by column chromatography on silica eluting with 7% MeOH/DCM

followed by preparative HPLC (Method B) to yield the title compound as a solid (1.5mg, 2.7%). TLC R<sub>f</sub> 0.05 (5% MeOH/DCM). LCMS 436 [M+H]<sup>+</sup>, RT 1.96 mins. <sup>1</sup>H NMR 400MHz (d<sub>4</sub>-MeOH) 8.50 (2H, 2xs), 8.20 (2H, 2xs), 7.35 (1H, s), 7.05 (1H, t), 6.50 (1H, s), 4.00 (3H, s), 3.85-3.75 (4H, m), 3.20 (3H, s), 2.80-2.70 (1H, m), 2.30-2.25 (1H, m).

**Example 83.**

**7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1-[[4-(trifluoromethyl)piperidin-1-yl]carbonyl]-1'H-spiro[pyrrolidine-3,2'-quinazolin]-4'(3'H)-one**

From Example 21 (50mg) and 4-(trifluoromethyl)piperidine (20mg). The residue was purified by column chromatography on silica eluting with 3-5% MeOH/DCM to yield the title compound as a yellow solid (27mg, 41%). TLC R<sub>f</sub> 0.67 (10% MeOH/DCM). LCMS 494 [M+H]<sup>+</sup>, RT 3.00 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.20 (2H, 2xs), 7.35 (1H, s), 6.50 (1H, s), 4.00 (3H, s), 3.85-3.70 (4H, m), 3.65-3.50 (2H, m), 3.15 (3H, s), 3.00-2.75 (2H, m), 2.70-2.55 (1H, m), 2.50-2.30 (1H, m), 2.25-2.15 (1H, m), 1.90-1.80 (2H, m), 1.60-1.40 (2H, m).

**Example 84.**

**4-[[{7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazolin]-1-yl]carbonyl}(methyl)amino]benzoic acid**

Example 74 (484mg), LiOH.H<sub>2</sub>O (161mg), THF (18ml), MeOH (9ml) and water (9ml) were combined and stirred at room temperature for 18 hours. The solvents were removed *in vacuo* and the residue triturated with 2N HCl to afford the title compound as a yellow solid (420mg). TLC R<sub>f</sub> 0.17 (EtOAc). LCMS 492 [M+H]<sup>+</sup>, RT 2.39 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.15 (1H, s), 8.1 (1H, s), 7.95 (2H, d), 7.3 (1H, s), 7.2 (2H, d), 6.4 (1H, s), 3.95 (3H, s), 3.5-3.25 (4H, m), 3.2 (3H, s), 3.0 (3H, s), 2.6-2.45 (1H, m), 2.1-2.0 (1H, m).

**Example 85.**

**7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1-pyridin-2-yl-1'H-spiro[pyrrolidine-3,2'-quinazolin]-4'(3'H)-one**

Example 21 (35mg), 2-chloropyridine, DBN (0.045ml) and DMF (3ml) were combined and heated to 120°C for 1.5 hours in a microwave reactor. The solvents were then removed *in vacuo* and the residue purified by preparative HPLC (Method A) to give the title compound as a glass (3mg). LCMS 392

[M+H]<sup>+</sup>, RT 1.57 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.45 (1H, s), 8.17 (1H, s), 8.15 (1H, s), 8.02 (1H, d), 7.55 (1H, m), 7.3 (1H, s), 6.65 (1H, m), 6.55 (1H, d), 6.45 (1H, s), 3.95 (3H, s), 3.85-3.65 (4H, m), 2.85-2.75 (1H, m), 2.35-2.3 (1H, m).

5 **Example 86.**

**N-Allyl-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

To a solution of Example 21 (70mg) in DCM (5ml) was added allyl isocyanate (0.017) and DIPEA (0.07ml). The reaction was stirred overnight and concentrated *in vacuo*. The residue was dissolved in DCM (100ml) and washed with 1N aqueous HCl (25ml). The organic layer was separated, dried over MgSO<sub>4</sub>, filtered and the solvent removed *in vacuo*. The resulting residue was triturated with Et<sub>2</sub>O to yield the title compound as a solid (49mg, 65%). TLC R<sub>f</sub> 0.12 (5% MeOH/DCM). LCMS 398 [M+H]<sup>+</sup>, RT 2.26 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.20 (1H, s), 7.38 (1H, s), 6.50 (1H, s), 5.91-5.79 (1H, m), 5.17-5.11 (1H, m), 5.06-5.03 (1H, m), 4.0 (3H, s), 3.79-3.74 (2H, m), 3.66-3.60 (4H, m), 3.12 (3H, s), 2.75-2.62 (1H, m), 2.27-2.16 (1H, m).

Examples 87 – 90 were prepared in a similar manner to the method of example 86:-

**Example 87.**

**N-Cyclopentyl-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

From Example 21 (70mg), DCM (5ml), cyclopentyl isocyanate (0.021ml) and DIPEA (0.07ml) to yield the title compound as a solid (60mg, 75%). TLC R<sub>f</sub> 0.15 (5% MeOH/DCM). LCMS 426 [M+H]<sup>+</sup>, RT 2.60 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.13 (1H, s), 8.13 (1H, s), 7.30 (1H, s), 6.46, (1H, s), 4.05-3.95 (1H, m), 3.92 (3H, s), 3.65-3.55 (4H, m), 3.10 (3H, s), 2.74-2.54 (1H, m), 2.25-2.12 (1H, m), 1.95-1.87 (2H, m), 1.74-1.30 (6H, m).

30 **Example 88.**

**Ethyl N-{[7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazolin]-1-yl]carbonyl}glycinate**

From Example 21 (70mg), DCM (5ml), ethyl isocyanatoacetate (0.021ml) and DIPEA (0.07ml) to yield the title compound as a solid (49mg, 58%). TLC R<sub>f</sub>

0.12 (5% MeOH/DCM). LCMS 444 [M+H]<sup>+</sup>, RT 2.26 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.20 (1H, s), 8.20 (1H, s), 7.38 (1H, s), 6.50 (1H, s), 4.25-4.15 (2H, q), 4.0 (3H, s), 3.88 (2H, s), 3.70-3.65 (4H, m), 3.17 (3H, s), 2.78-2.62 (1H, m), 2.30-2.20 (1H, m), 1.29-1.22 (3H, t).

5 **Example 89.**

**N-Benzoyl-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

From Example 21 (70mg), DCM (5ml), benzoyl isocyanate (0.024ml) and DIPEA (0.07ml) to yield the title compound as a solid (57mg, 65%). TLC R<sub>f</sub>

10 0.13 (5% MeOH/DCM). LCMS 462 [M+H]<sup>+</sup>, RT 2.50 mins. <sup>1</sup>H NMR 300MHz (d<sub>6</sub>-DMSO) 8.31 (1H, s), 7.99 (1H, s), 7.90-7.70 (2H, m), 7.65-7.55 (2H, m), 7.50-7.40 (2H, m), 7.32 (1H, s), 6.50 (1H, s), 3.95 (3H, s), 3.95-3.55 (4H, m), 3.00 (3H, s), 2.65-2.55 (1H, m), 2.18-2.05 (1H, m).

**Example 90.**

15 **N-(3,5-Dimethylisoxazol-4-yl)-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

From Example 21 (70mg), DCM (5ml), 3,5-dimethyl isoxazol-4-yl isocyanate (26mg) and DIPEA (0.07ml) to yield the title compound as a solid (19mg,

20 22%). TLC R<sub>f</sub> 0.09 (5% MeOH/DCM). LCMS 453 [M+H]<sup>+</sup>, RT 2.22 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.21 (1H, s), 8.21 (1H, s), 7.35 (1H, s), 6.52 (1H, s), 4.00 (3H, s), 3.75 (4H, m), 3.18 (3H, s), 2.85-2.65 (1H, m), 2.32-2.26 (1H, m), 2.28 (3H, s), 2.15(3H, s).

25 Examples 91-99 were prepared in a similar manner to the method of example 62:-

**Example 91.**

**7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-N-3-thienyl-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

30 From Example 21 (25mg) and 3-aminothiophene (12mg). The resulting solid was obtained by filtration to yield the title compound as a white solid (10.1mg, 33%). LCMS 440 [M+H]<sup>+</sup>, RT 2.64 mins. <sup>1</sup>H NMR 300MHz (d<sub>6</sub>-DMSO) 8.65 (1H, s), 8.40 (1H, s), 8.05 (1H, s), 7.60 (1H, s), 7.40 (2H, m), 7.30 (1H, d),

7.15 (1H, d), 6.60 (1H, s), 3.95 (3H, s), 3.70-3.60 (4H, m), 3.10 (3H, s), 2.75-2.60 (1H, m), 2.20-2.10 (1H, m).

**Example 92.**

**N-(Cyclopropylmethyl)-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

From Example 21 (50mg) and aminomethylcyclopropane (11□l). The residue was purified by preparative HPLC (Method B) to yield the title compound as a white solid (20mg, 37%). TLC R<sub>f</sub> 0.11 (5% MeOH/DCM). LCMS 412 [M+H]<sup>+</sup>, RT 2.39 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.20(2H, 2xs), 7.35 (1H, s), 6.50 (1H, s), 4.00 (3H, s), 3.60-3.70 (2H, m), 3.15 (3H, s), 3.05 (2H, d), 2.60- 2.80 (1H, m), 0.90-1.10 (1H, m), 0.40-0.50 (2H, m), 0.10-0.20 (2H, m).

**Example 93.**

**7'-Methoxy-N,3'-dimethyl-6'-(1,3-oxazol-5-yl)-4'-oxo-N-(2-phenylethyl)-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

From Example 21 (50mg) and N-methylphenethylamine (18mg) using pyridine (33mg). The residue was purified by column chromatography on silica eluting with 2-4% MeOH/DCM followed by preparative HPLC (Method B) to yield the title compound as a white solid (2.3mg, 15%). TLC R<sub>f</sub> 0.43 (5% MeOH/DCM). LCMS 476 [M+H]<sup>+</sup>, RT 2.98 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.15(2H, 2xs), 7.35 (1H, s), 7.05-7.20 (5H, m), 6.55 (1H, s), 3.95 (3H, s), 3.50-3.70 (3H, m), 3.25-3.45 (3H, m), 3.10 (3H, s), 2.75—2.85 (4H, m), 2.45-2.60 (1H, m), 2.05-2.15 (2H, m).

**Example 94.**

**7'-Methoxy-N,3'-dimethyl-N-[2-(methylsulfonyl)ethyl]-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

From Example 21 (80mg) and (2-methanesulfonyl-ethyl)methylamine (CAS 202198-18-3) (28mg) using pyridine (33mg). The residue was purified by preparative HPLC (Method B) to yield the title compound as a white solid (9mg, 9%). LCMS 478 [M+H]<sup>+</sup>, RT 2.12 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.20 (2H, 2xs), 7.35 (1H, s), 6.50 (1H, s), 3.95 (3H, s), 3.55-3.85 (4H, m), 3.35-3.45 (4H, m), 3.15 (3H, s), 2.95 (6H, 2xs), 2.55-2.70 (1H, m), 2.10-2.25 (2H, m).

**Example 95.**

**N,7'-Dimethoxy-N,3'-dimethyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

From Example 21a (80mg) and *N,O*-dimethylhydroxylamine hydrochloride (22mg) using diisopropylethylamine (141mg). The residue was by preparative HPLC (Method A) to yield the title compound as a white solid (27.7mg, 32%). TLC  $R_f$  0.37 (5% MeOH/DCM). LCMS 402  $[M+H]^+$ , RT 2.37 mins.  $^1H$  NMR 300MHz ( $d_4$ -MeOH) 8.20 (2H, s), 7.40 (1H, s), 6.50 (1H, s), 4.00 (3H, s), 3.70-3.90 (4H, m), 3.65 (3H, s), 3.20 (3H, s), 3.00 (3H, s), 2.60-2.75 (1H, m), 2.15-2.35 (2H, m).

**Example 96.**

**N-[2-(Dimethylamino)ethyl]-7'-methoxy-N,3'-dimethyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

From Example 21a (50mg) and *N,N,N'*-trimethylethylenediamine (13mg). The residue was purified by column chromatography on silica eluting with DCM/MeOH/*c.NH*<sub>4</sub>OH (90:9:1) to give the title compound as a pale green glass (3.2mg, 6%). TLC  $R_f$  0.32 (9% MeOH/DCM + trace *c.NH*<sub>4</sub>OH). LCMS 443  $[M+H]^+$ , RT 1.50 mins.  $^1H$  NMR 300MHz ( $d_4$ -MeOH) 8.17-8.18 (2H, 2 x s), 7.32 (1H, s), 6.47 (1H, s), 3.97 (3H, s), 3.33-3.82 (6H, m), 3.12 (3H, s), 2.90 (3H, s), 2.56-2.67 (1H, m), 2.51 (2H, t), 2.26 (3H, s), 2.10-2.20 (1H, m).

**Example 97.**

**N-Cyclopropyl-N-ethyl-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

From Example 21a (50mg) and the hydrochloride salt of *N*-cyclopropyl-*N*-ethylamine (CAS 26389-72-0) (16mg). The residue was purified by preparative HPLC (Method B) to give the title compound (11mg, 20%). TLC  $R_f$  0.35 (10% MeOH/DCM). LCMS 426  $[M+H]^+$ , RT 2.60 mins.  $^1H$  NMR 300MHz ( $CDCl_3$ ) 8.32 (1H, s), 7.88 (1H, s), 7.48 (1H, s), 6.24 (1H, s), 5.00 (1H, brs), 3.75-3.92 (4H, m), 3.40-3.65 (4H, m), 3.06-3.18 (4H, m), 2.45-2.58 (2H, m), 2.14-2.23 (1H, m), 1.11 (3H, t), 0.60-0.88 (4H, m).

**Example 98.**

**N-(2-Cyanoethyl)-N-isopropyl-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

From Example 21a (53mg) and 3-(isopropylamino)propionitrile (CAS 692-98-8) (16mg). The residue was purified by preparative HPLC (Method B) to give the title compound (43mg, 68%). LCMS 453 [M+H]<sup>+</sup>, RT 2.53 mins. <sup>1</sup>H NMR 300MHz (CDCl<sub>3</sub>) 8.32 (1H, s), 7.87 (1H, s), 7.38 (1H, s), 6.27 (1H, s), 4.92 (1H, s), 3.93 (3H, s), 3.75-3.86 (4H, m), 3.42-3.59 (2H, m), 3.20-3.30 (1H, m), 3.16 (3H, s), 2.60-2.65 (2H, m), 2.41-2.52 (1H, m), 2.20-2.29 (1H, m), 1.20 (3H, d), 1.17 (3H, d).

**Example 99.**

**N-[2-(Acetylamino)ethyl]-7'-methoxy-N,3'-dimethyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

From Example 21a (50mg) and N-[2-(methylamino)ethyl]acetamide (CAS 4814-81-7) (15mg). The residue was purified by preparative HPLC (Method B) to give the title compound (19mg, 32%). TLC R<sub>f</sub> 0.45 (10% MeOH/DCM). LCMS 457 [M+H]<sup>+</sup>, RT 2.01 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.2 (2H, 2 x s), 7.36 (1H, s), 6.52 (1H, s), 3.99 (3H, s), 3.70-3.80 (2H, m), 3.53-3.62 (2H, m), 3.24-3.46 (4H, m), 3.15 (3H, s), 2.91 (3H, s), 2.57-2.68 (1H, m), 2.15-2.23 (1H, m), 1.89 (3H, s).

**Example 100.**

**7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1'H,2H-spiro[pyrrolidine-3,2'-quinazoline]-2,4'(3'H)-dione**

To a solution of Intermediate 6 (25mg) in MeOH (10ml) was added a catalytic amount of 10% Pd/C. The solution was stirred at room temperature under hydrogen for 3.5 hours. The reaction mixture was filtered to remove catalyst and solvents removed under reduced pressure to give the title compound (18mg, 100%). LCMS 329 [M+H]<sup>+</sup>, RT 1.93 mins.

**Example 101.**

**1-Benzyl-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1'H,2H-spiro[pyrrolidine-3,2'-quinazoline]-2,4'(3'H)-dione**

To a solution of Example 100 (90mg) in DMF (10ml) was added sodium hydride (11mg). The solution was stirred under nitrogen for 90 mins at which point benzylbromide (0.03ml) was added. The solution was stirred for 18 hours. The solvents were removed *in vacuo* and the product purified by preparative HPLC (Method A) to give the title compound as a beige solid (11mg, 10%). LCMS



419 [M+H]<sup>+</sup>, RT 2.81 mins. <sup>1</sup>H NMR 400MHz (d<sub>4</sub>-MeOD) 8.15 (1H, s), 8.10 (1H, s), 7.40-7.30 (6H, m), 6.35 (1H, s), 4.60 (1H, d), 4.40 (1H, d), 3.95 (3H, s), 3.50-3.30 (2H, m), 2.90 (3H, s), 2.75-2.65 (1H, m), 2.35-2.25 (1H, m).

- 5 Examples 102, 103 and 104 describe the preparation of three out of the four diastereomers of 1-*tert*-butyl 5-methyl 7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1*H*,1'*H*-spiro[pyrrolidine-3,2'-quinazoline]-1,5-dicarboxylate.

**Example 102.**

- 10 **1-*tert*-Butyl 5-methyl 7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1*H*,1'*H*-spiro[pyrrolidine-3,2'-quinazoline]-1,5-dicarboxylate (Diastereomer 1)**

- To a solution of Intermediate 1 (300mg) in dry DCE (30ml) under nitrogen was added 1-*tert*-butyl 2-methyl (2*S*)-4-oxopyrrolidine-1,2-dicarboxylate (300mg) and PTSA (5mg). The mixture was heated at reflux for 5 hours. The reaction mixture was diluted with DCM (100ml) and washed with H<sub>2</sub>O (50ml). The organic layer was separated, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica eluting with EtOAc to afford the title compound along with Example 103 as a pale yellow solid (420mg, 73%). A portion of this mixture was separated into its component diastereomers by preparative HPLC (Method A) to afford Diastereomer 1 as a cream solid (197mg). TLC R<sub>f</sub> 0.29 (EtOAc). LCMS 473 [M+H]<sup>+</sup>, RT 3.25 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.21 (1H, s), 8.18 (1H, s), 7.38 (1H, s), 6.41 (1H, s), 4.54-4.48 (1H, dd), 4.05-4.02 (1H, d), 4.02 (3H, s), 3.80 (3H, s), 3.72-3.68 (1H, d), 3.12 (3H, s), 3.04-2.88 (1H, m), 2.35-2.25 (1H, m), 1.49 and 1.45 (9H, 2xs).

**Example 103.**

- 1-*tert*-Butyl 5-methyl 7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1*H*,1'*H*-spiro[pyrrolidine-3,2'-quinazoline]-1,5-dicarboxylate (Diastereomer 2)**

Following the procedure described for Example 102; Diastereomer 2 was also isolated as an off-white solid (41mg). TLC R<sub>f</sub> 0.29 (EtOAc). LCMS 473 [M+H]<sup>+</sup>, RT 3.15 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.21 (1H, s), 8.19 (1H,

s), 7.38 (1H, s), 6.51 (1H, s), 4.57-4.50 (1H, m), 4.00 (3H, s), 3.83 (3H, s), 3.83-3.72 (2H, m), 3.15 (3H, s), 2.67-2.50 (2H, m), 1.45 (9H, s).

#### **Example 104.**

5 **1-tert-Butyl 5-methyl 7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1,5-dicarboxylate (Diastereomer 3)**

A solution of Intermediate 1 (700mg), 1-tert-butyl 2-methyl-(2R)-4-oxopyrrolidine-1,2-dicarboxylate (CAS 256487-77-1) (720mg) and PTSA (5mg) in dry DCE (40ml) was heated at reflux for 18 hours. The reaction mixture was diluted with DCM (100ml) and washed with aqueous 2M HCl (40ml). The organic layer was separated, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by preparative HPLC (Method A) to afford Diastereomer 3 as a single diastereomer as an off-white solid (635mg, 47%). TLC R<sub>f</sub> 0.35 (EtOAc). LCMS 473 [M+H]<sup>+</sup>, RT 3.26 mins.  
15 <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.21 (1H, s), 8.18 (1H, s), 7.38 (1H, s), 6.41 (1H, s), 4.54-4.48 (1H, dd), 4.05-4.02 (1H, d), 4.02 (3H, s), 3.80 (3H, s), 3.72-3.68 (1H, d), 3.12 (3H, s), 3.04-2.88 (1H, m), 2.35-2.25 (1H, m), 1.49 and 1.45 (9H, 2xs).

#### **Example 105.**

20 **1-tert-Butyl 5-isopropyl 7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1,5-dicarboxylate**

From Intermediate 1 (160mg) and Intermediate 9 (190mg). Purification by preparative HPLC (Method A) afforded the title compound as a single diastereomer as a pale orange solid (137mg, 42%). TLC R<sub>f</sub> 0.51 (EtOAc).  
25 LCMS 501 [M+H]<sup>+</sup>, RT 3.66 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.21 (1H, s), 8.19 (1H, s), 7.36 (1H, s), 6.40 (1H, s), 5.14-5.02 (1H, hep), 4.46-4.39 (1H, m), 4.07-4.03 (1H, d), 3.99 (3H, s), 3.73-3.68 (1H, d), 3.13 (3H, s), 3.03-2.88 (1H, m), 2.32-2.20 (1H, m), 1.49 and 1.45 (9H, 2xs), 1.34-1.31 (3H, d), 1.25-1.22 (3H, m).

30 **Example 106.**

**1-(tert-Butoxycarbonyl)-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1'H-spiro[pyrrolidine-3,2'-quinazoline]-5-carboxylic acid**

To a solution of Example 104 (100mg), in THF (3ml) and water (3ml), stirring at room temperature was added LiOH.H<sub>2</sub>O (9mg). The reaction mixture was

stirred for 2.5 hours before being concentrated *in vacuo*, neutralised with aqueous 1M HCl solution and extracted with EtOAc (3x20ml). The organic layers were combined, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to yield the title compound as a single diastereomer as an off-white solid 50.5mg (52%). HPLC RT 2.78. LCMS 459 [M+H]<sup>+</sup>, RT 2.84 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.19 (1H, s), 8.17 (1H, s), 7.35 (1H, s), 6.37 (1H, s), 4.45-4.36 (1H, m), 4.00-3.93 (4H, m), 3.74-3.63 (1H, m), 3.10 (3H, s), 3.03-2.97 (1H, m), 2.33-2.22 (1H, m), 1.47-1.40 (9H, m).

- 10 Examples 107 and 108 describe the preparation of two out of the four diastereomers of *tert*-butyl 7'-methoxy-3'-methyl-5-(3-methyl-1,2,4-oxadiazol-5-yl)-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1*H*,1'*H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxylate.

**Example 107.**

- 15 ***tert*-Butyl 7'-methoxy-3'-methyl-5-(3-methyl-1,2,4-oxadiazol-5-yl)-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1*H*,1'*H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxylate (Diastereomer 1)**

- To a solution of (1*Z*)-*N*-hydroxyethanimidamide (CAS 140461-42-3) (20mg) in dry THF (5ml) under nitrogen was added sodium hydride (60% dispersion in mineral oil, 11mg) and the mixture heated at reflux for 90 mins. A solution of Example 104 was then added and the reaction mixture heated at reflux for 18 hours. The mixture was concentrated *in vacuo* and H<sub>2</sub>O (30ml) added to the residue. This was extracted with DCM (2x75ml) and the organic layers combined, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*, to give a mixture of two diastereomers. Purification by column chromatography on silica eluting with EtOAc followed by preparative HPLC (Method A) afforded Diastereomer 1 as a white solid (4.8mg, 9%). TLC R<sub>f</sub> 0.29 (EtOAc). LCMS 498 [M+H]<sup>+</sup>, RT 3.28 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.22 (1H, s), 8.20 (1H, s), 7.38 (1H, s), 6.38 (1H, s, br), 5.31-5.28 (1H, dd), 4.19-4.15 (1H, d), 3.98 (3H, s), 3.83-3.79 (1H, d), 3.18 (3H, s), 3.18-3.03 (1H, m), 2.50-2.37 (1H, m), 2.45 (3H, s), 1.50 and 1.35 (9H, 2xs).

**Example 108.**

**tert-Butyl 7'-methoxy-3'-methyl-5-(3-methyl-1,2,4-oxadiazol-5-yl)-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxylate (Diastereomer 2).**

Following the procedure described for Example 107; Diastereomer 2 was also  
5 isolated as an off-white solid (1.5mg, 3%). TLC R<sub>f</sub> 0.18 (EtOAc). LCMS 498 [M+H]<sup>+</sup>, RT 3.13 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.20 (2H, 2xs), 7.38 (1H, s), 6.54 (1H, s), 5.34-5.25 (1H, m), 4.01 (3H, s), 3.98 (2H, s), 3.16 (3H, s), 2.76-2.73 (1H, m), 2.40 (3H, s), 1.40 and 1.25 (9H, 2xs).

**Example 109.**

10 **tert-Butyl 7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-5-(pyrrolidin-1-ylcarbonyl)-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxylate**

To a stirring solution of Example 106 (44mg), HBTU (36mg), and DIPEA (0.09ml) in DMF (2ml) was added pyrrolidine (0.02ml). The reaction mixture  
15 was stirred at room temperature for 18 hours concentrated *in vacuo* and the residue purified by column chromatography on silica eluting with 2% MeOH/DCM, to yield the title compound as a single diastereomer as a solid 18mg (37%). TLC R<sub>f</sub> 0.24 (2%MeOH/DCM). LCMS 512 [M+H]<sup>+</sup>, RT 3.14 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.17 (1H, s), 8.15 (1H, s), 7.34 (1H, s),  
20 6.43 (1H, s), 4.73-4.66 (1H, m), 3.98 (3H, s), 3.86-3.35 (6H, m), 3.12 (3H, s), 3.05-2.92 (1H, m), 2.22-2.11 (1H, m), 2.05-1.85 (4H, m), 1.45-1.35 (9H, m).

**Example 110.**

**tert-Butyl 5-[(dimethylamino)carbonyl]-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxylate**

To a stirring solution of Example 106 (70mg), EDC (29mg), HOBt (21mg) and TEA (0.06ml) in DCM (5ml), was added dimethylamine hydrochloride (25mg). The mixture was stirred at room temperature overnight. More dimethylamine hydrochloride (25mg) and TEA (0.03ml) were added to the reaction mixture,  
30 which was left to stir at room temperature overnight. DMAP (1mg) was added to the reaction mixture, which was left to stir at room temperature overnight. The mixture was concentrated *in vacuo* and the residue purified by column chromatography on silica eluting with 4%MeOH/DCM to yield the title compound as a single diastereomer as a white solid 5.3mg (7%). HPLC RT

2.92 minutes. LCMS 486 [M+H]<sup>+</sup>, RT 2.92 mins. <sup>1</sup>H NMR 300MHz (d<sub>6</sub>-DMSO, 130°C) 8.13 (1H, s), 7.99 (1H, s), 7.25 (1H, s), 7.23 (1H, s, br), 6.35 (1H, s), 4.87-4.80 (1H, m), 3.94 (3H, s), 3.93-3.90 (1H, d), 3.66-3.63 (1H, d), 3.05 (3H, s), 3.00 (6H, s), 2.95-2.90 (1H, m), 2.10-2.05 (1H, m), 1.40 (9H, m).

5 **Example 111.**

**Methyl 7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1'H-spiro[pyrrolidine-3,2'-quinazoline]-5-carboxylate hydrochloride**

To a solution of Example 104 in dry DCM (2ml) under nitrogen cooled to 0°C was added a solution of HCl in Et<sub>2</sub>O (1.0M, 20ml). The reaction mixture was  
10 allowed to warm to room temperature and stirred for 2 hours. The resulting solid was filtered off, washed with copious quantities of Et<sub>2</sub>O and dried *in vacuo* to afford the title compound as a single diastereomer as an off-white solid (80mg, 92%). LCMS 373 [M-HCl+H]<sup>+</sup>, RT 1.50 mins. <sup>1</sup>H NMR 400MHz after aqueous NaHCO<sub>3</sub> shake. (CDCl<sub>3</sub>) 8.31 (1H, s), 7.88 (1H, s), 7.38 (1H, s),  
15 6.18 (1H, s), 4.02-3.97 (1H, m), 3.95 (3H, s), 3.78 (3H, s), 3.36-3.33 (1H, d), 3.30-3.27 (1H, d), 2.58-2.52 (1H, m), 2.26-2.22 (2H, d).

**Example 112.**

**Methyl 1-(2-furoyl)-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1'H-spiro[pyrrolidine-3,2'-quinazoline]-5-carboxylate**

20 To a solution of 2-furoic acid (13mg) in DCM (5ml) stirring under nitrogen at room temperature was added EDC (23mg), TEA (0.06ml) and HOBt (16.2mg). The mixture was stirred at room temperature for 30 minutes before adding Example 10 (49mg). The reaction mixture was allowed to stir at room temperature for another 48 hours. DMAP (2mg) was added and the mixture  
25 stirred for 18 hours and concentrated *in vacuo*. Purification was by preparative HPLC (Method B) followed by column chromatography on silica eluting with 4% MeOH/DCM to give the title compound as a single diastereomer as a white solid (2.5mg, 4.5%). TLC R<sub>f</sub> 0.15 (4% MeOH/DCM). LCMS 467 [M+H]<sup>+</sup>, RT 2.65 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.20 (2H, s), 7.74 (1H, s),  
30 7.35 (1H, s) 7.20 (1H, m), 7.12 (1H, d), 6.53 (1H, m), 6.60 (1H, m), 6.38 (1H, s) 4.90-4.80 (1H, m), 4.58-4.50 (1H d), 4.37-4.30 (1H, d), 4.00 (3H, s), 3.80 (3H, s), 3.15 (3H, s) 3.05-2.95 (1H, m), 2.35-2.25 (1H, m).

**Example 113.****1-Ethyl 5-methyl 7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1,5-dicarboxylate**

To a solution of Example 111 (49mg) in DCM (5ml), stirring under nitrogen at 0°C was added TEA (0.05ml) followed by ethylchloroformate (0.013ml). The mixture was allowed to warm slowly to room temperature. The reaction mixture was diluted with water ((20ml) and extracted into DCM (3x50ml). The organic layers were combined, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. Purification by column chromatography on silica eluting with 2% MeOH/DCM afforded the title compound as a single diastereomer as an off-white solid (35.7mg, 67%). HPLC RT 2.77 mins. LCMS 445 [M+H]<sup>+</sup>, RT 2.79 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.18 (1H, s), 8.15 (1H, s), 7.34 (1H, s) 6.34 (1H, s), 4.58-4.50 (1H, m), 4.20-4.05 (3H, m), 3.98 (3H, s) 3.77 (3H, m), 3.76-3.70 (1H d), 3.10 (3H, s), 3.02-2.90 (1H, m), 2.35-2.24(1H, m), 1.30-1.15 (3H, m).

Example 114 was prepared in a similar manner to the method of Example 12:-

**Example 114.****1-iso-Propyl 5-methyl 7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1H,1'H-spiro[pyrrolidine-3,2'-quinazoline]-1,5-dicarboxylate**

From Example 111 (50mg) and *iso*-propylchloroformate. The residue was purified by column chromatography on silica eluting with 2% MeOH/DCM to yield the title compound as a single diastereomer as a yellow solid, (41.7mg, 62%). HPLC RT 2.99 mins. LCMS 459 [M+H]<sup>+</sup>, RT 3.01 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.17 (2H, 2xs), 7.33 (1H, s), 6.39 (1H, s) 4.92-4.82(1H, m), 4.55-4.47 (1H, m), 4.12-4.02 (1H, d), 3.97 (3H, s), 3.79 (3H, s), 3.75-3.69 (1H, d), 3.11 (3H, s), 3.01-2.89 (1H, m), 2.35-2.22(1H, m), 1.27-1.22 (6H, m).

**Example 115.****Methyl 7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-1-(piperidin-1-ylcarbonyl)-3',4'-dihydro-1'H-spiro[pyrrolidine-3,2'-quinazoline]-5-carboxylate**

To a suspension of Example 111 (65mg) in dry DCM (10ml) under N<sub>2</sub> cooled to 0°C was added dropwise 1-piperidinecarbonyl chloride (0.024ml) followed

by TEA (0.05ml), again dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 4 hours. The mixture was concentrated *in vacuo* and the residue purified by column chromatography on silica eluting with 5% MeOH/DCM to afford the title compound as a single diastereomer as a pale yellow solid (50mg, 65%). LCMS 484 [M+H]<sup>+</sup>, RT 2.85 mins. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>-MeOH) 8.22 (1H, s), 8.20 (1H, s), 7.40 (1H, s), 6.46 (1H, s), 4.85-4.78 (1H, tr), 4.01-3.95 (1H, d), 3.99 (3H, s), 3.82-3.76 (1H, d), 3.78 (3H, s), 3.40-3.20 (2H, m), 3.12-3.01 (1H, m), 3.07 (3H, s), 2.30-2.23 (1H, dd), 1.72-1.50 (6H, m).

10 **Example 116.**

**Methyl 7'-methoxy-3'-methyl-1-{[methyl(phenyl)-amino]carbonyl}-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1'H-spiro[pyrrolidine-3,2'-quinazoline]-5-carboxylate**

To a solution of *N*-methylaniline (0.01ml) and pyridine (0.03ml) in DCM (5ml), stirring under nitrogen at -78°C, was added triphosgene (17mg). The reaction mixture was stirred at 0°C for 30 minutes before adding Example 111 (50mg) and pyridine (0.03ml). The mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was purified by column chromatography on silica eluting with EtOAc followed by 5% MeOH/DCM to yield the title compound as a single diastereomer as a white solid, (6.4mg, 10%). TLC R<sub>f</sub> 0.41 (EtOAc). LCMS 506 [M+H]<sup>+</sup>, RT 2.91 mins. <sup>1</sup>H NMR 300MHz (d<sub>6</sub>-DMSO) 8.33 (1H, s, br), 7.88 (1H, s), 7.40-7.12 (8H, m), 6.24 (1H, s), 4.65-4.75 (1H, m), 4.85 (3H, s), 3.70 (3H, s), 3.58-3.50 (1H, d), 3.13 (3H, s), 3.98-2.78 (5H, s), 2.05-1.93 (1H, m).

Example 117 was prepared in a similar manner to the method of Example 116:-

**Example 117.**

**Methyl 7'-methoxy-1-{[methoxy(methyl)amino]carbonyl}-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1'H-spiro[pyrrolidine-3,2'-quinazoline]-5-carboxylate**

From Example 111 (50mg) and *N,O*-dimethylhydroxylamine hydrochloride (14mg). Purification by column chromatography on silica eluting with 2% MeOH/DCM afforded the title compound as a brown solid, 14.4mg (21%).

HPLC RT 2.53 minutes. LCMS 460 [M+H]<sup>+</sup>, RT 2.57 minutes. <sup>1</sup>H NMR 300MHz (d<sub>4</sub>MeOD) 8.20 (1H, s, br), 8.18 (1H, s), 7.38 (1H, s, br), 6.40 (1H, s) 4.73-4.65(1H, m), 4.23-4.16 (1H, d), 4.00 (3H, s), 3.90-3.86 (1H, d), 3.76 (3H, s), 3.62 (3H, s), 3.11 (3H, s), 3.05 (3H, s), 3.03-2.96(1H, m), 2.25-2.17 (1H, m).

Example 118 describes the preparation of a mixture of two out of the four diastereomers of 1-*tert*-butyl 5-methyl 7'-methoxy-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1*H*,1'*H*-spiro[pyrrolidine-3,2'-quinazoline]-1,5-dicarboxylate, and was prepared in a similar manner to the method of example 104:-

#### **Example 118.**

#### **1-*tert*-Butyl 5-methyl 7'-methoxy-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-1*H*,1'*H*-spiro[pyrrolidine-3,2'-quinazoline]-1,5-dicarboxylate**

From Intermediate 2 (193mg) and 1-*tert*-butyl 2-methyl (2*S*)-4-oxopyrrolidine-1,2-dicarboxylate (211mg). The residue was purified by column chromatography on silica eluting with 5% MeOH/DCM to yield the title compound as a beige solid (297mg, 78%). TLC R<sub>f</sub> 0.32 (5% MeOH/DCM). LCMS 459 [M+H]<sup>+</sup>, RT 3.38 mins. <sup>1</sup>H NMR 400MHz (d<sub>4</sub> MeOH) 8.16 (1H, s), 8.13 (1H, s), 7.34 (1H, s), 6.45 and 6.39 (1H, 2xs), 4.43-4.51 (1H, m), 3.99 (3H, s), 3.76-3.79 (4H, m), 3.51-3.58 (1H, m), 2.60-2.70 (1H, m), 2.19-2.29 (1H, m), 1.44 and 1.40 (9H, 2xs).

The ability of the compounds of the invention to inhibit the IMPDH enzymes may be determined using the following assays:

#### **Abbreviations used:**

IMPDH Inosine 5'monophosphate dehydrogenase

IMP Inosine 5'monophosphate XMP Xanthosine 5'-monophosphate

NAD β- Nicotinamide adenine dinucleotide

NADH β- Nicotinamide adenine dinucleotide, reduced form

MTT 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide

#### **Assay Protocol 1**

IMPDH catalyses the NAD dependent oxidation of IMP to XMP with concomitant reduction of the coenzyme. IMPDH activity was determined by



monitoring the production of the fluorescent product, NADH. Assays were performed in a final volume of 200 $\mu$ l containing IMPDH (2 $\mu$ g), NAD (100 $\mu$ M), IMP (100 $\mu$ M), 1% DMSO, 30mM KCl and 100mM Tris/HCl, pH7.5. Fluorescence (excitation 340nm / emission 465nm) was read continuously at 25°C for 30 minutes. From this data, initial rates (i.e. change in fluorescence intensity per minute) were calculated. To determine the IC<sub>50</sub> values, test compounds were prepared at an initial concentration of 1.0mM in 100% DMSO, then diluted in assay buffer to 0.2mM. Further dilutions were made in assay buffer containing 20% DMSO, prior to diluting 20-fold into the assay, to allow testing across the range 0.3nM to 10 $\mu$ M.

The functional effect of the compounds of the invention may be demonstrated using the following assay:

**PBMC Proliferation Assay**

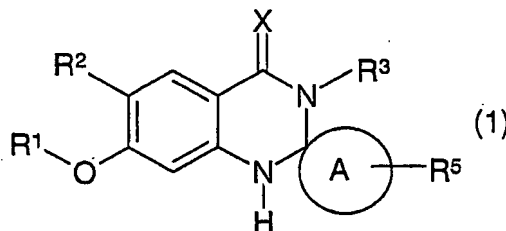
Peripheral blood mononuclear cells were isolated from freshly taken human blood using standard procedures. Cells were plated out in RPMI medium containing 5% human serum in the presence and absence of inhibitor. PHA (25 $\mu$ l of 30 $\mu$ g/ml solution to each well) was added and the plates were incubated at 37°C in an atmosphere of 95% air/5% CO<sub>2</sub> for 48 hours. 0.5 $\mu$ Ci of tritiated thymidine was added to each well and the plates were incubated for a further 18 hours. The contents of the plate were transferred to a filter plate and the cells washed with saline. The plates were dried, microscintillation fluid was added to each well and the plate was counted on a scintillation counter. IC<sub>50</sub> values were calculated by plotting inhibitor concentration versus %inhibition.

The assay described above can be carried out using anti-CD3 (40 $\mu$ l of 3750ng/ml concentration to each well) stimulation instead of PHA.

Compounds of each of the Examples inhibit IMPDH enzymes with IC<sub>50</sub> values of 5 $\mu$ M or below.

**CLAIMS**

1. A compound of formula (1):



5

wherein:

X is an oxygen or sulfur atom;

R¹ is an aliphatic, cycloaliphatic or cycloalkyl-alkyl- group;

R² is an optionally substituted heteroaromatic group or a -CN group;

10 R³ is a group  $-(Alk^1)_m L^1 (Alk^2)_n R^4$  in which m and n, which may be the same or different, is each zero or the integer 1, Alk¹ and Alk², which may be the same or different, is each an optionally substituted aliphatic or heteroaliphatic chain, L¹ is a covalent bond or a linker atom or group and R⁴ is a hydrogen atom or an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group;

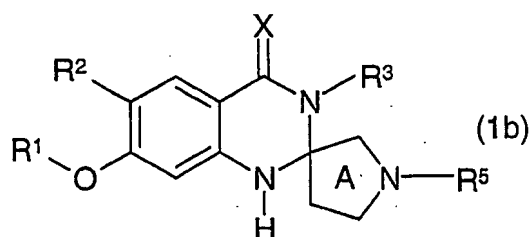
15 A is an optionally substituted cycloaliphatic or heterocycloaliphatic group optionally fused to an optionally substituted aryl or heteroaryl group;

20 R⁵, which may be attached to any available C or N atom present in the cycloaliphatic or heterocycloaliphatic, or where fused, aryl or heteroaryl group, is a group  $-(Alk^3)_t L^2 (Alk^4)_v R^6$  in which t and v, which may be the same or different, is each zero or the integer 1, Alk³ and Alk⁴, which may be the same or different, is each an optionally substituted aliphatic or heteroaliphatic chain, L² is a covalent bond or a linker atom or group and R⁶ is a hydrogen or halogen atom or a -CN group or an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group;

25 and the salts, solvates, hydrates, tautomers, isomers or N-oxides thereof.

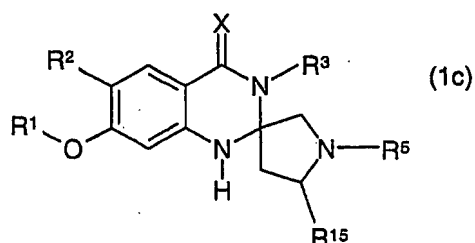
2. A compound according to Claim 1 in which Alk¹, Alk², Alk³ or Alk⁴, when present in compounds of formula (1), may be the same or different, and is each an optionally substituted C₁-₆ alkylene chain.

3. A compound according to Claim 1 or Claim 2 wherein  $R^3$  is a group  $-(Alk^1)_m L^1 (Alk^2)_n R^4$  and  $R^5$  is a group  $-(Alk^3)_t L^2 (Alk^4)_v R^6$  in which  $L^1$  or  $L^2$  is covalent bond or an atom or group selected from -O- or -S- atoms or -C(O)-, -C(S)-, -S(O)-, -S(O)<sub>2</sub>-, -C(O)O-, -OC(O)-, -N(R<sup>7</sup>)- [where R<sup>7</sup> is a hydrogen atom or a straight or branched C<sub>1-6</sub>alkyl group], -CON(R<sup>7</sup>)-, -CSN(R<sup>7</sup>)-, -N(R<sup>7</sup>)CO-, -N(R<sup>7</sup>)CS-, -S(O)<sub>2</sub>N(R<sup>7</sup>)- or -N(R<sup>7</sup>)S(O)<sub>2</sub>- groups.
4. A compound according to any one of Claims 1 - 3 in which  $R^3$  is the group  $-Alk^1-L^1-R^4$ .
5. A compound according to any one of Claims 1 - 4 in which  $R^3$  is a C<sub>1-6</sub> alkyl group.
6. A compound according Claim 5 in which  $R^3$  is a methyl group.
7. A compound according to any one of Claims 1 - 4 in which  $R^3$  is a hydrogen atom.
8. A compound according to any one of Claims 1 - 7 in which X is an O atom.
9. A compound according to any one of Claims 1 - 8 wherein  $R^1$  is a C<sub>1-6</sub> alkyl group.
10. A compound according to Claim 9 wherein  $R^1$  is a methyl group.
11. A compound according to any one of Claims 1 - 10 wherein  $R^2$  is a five-membered heteroaromatic group containing one, two, three or four heteroatoms selected from oxygen, sulfur or nitrogen.
12. A compound according to Claim 11 wherein  $R^2$  is an oxazolyl group.
13. A compound according to any one of Claims 1 - 12 wherein A is optionally substituted C<sub>3-6</sub> cycloaliphatic group or 3 to 6 membered saturated monocyclic hydrocarbon ring system containing one or two L<sup>4</sup> linker atoms or groups, optionally fused to an optionally substituted phenyl or monocyclic C<sub>1-6</sub> heteroaromatic group containing one, two, three or four heteroatoms selected from oxygen, sulfur or nitrogen.
14. A compound according to any one of claims 1 - 13 which has the formula (1b):



in which A is an optionally substituted pyrrolidinyl ring; R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>5</sup> and X are as defined herein.

15. A compound according to any one of claims 1- 14 which has the formula  
5 (1c):



wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>5</sup> and X are defined herein; R<sup>15</sup> is a group selected from  
-CN, -CO<sub>2</sub>R<sup>10a</sup> [where R<sup>10a</sup> is a hydrogen atom or a C<sub>1-6</sub>alkyl group], -  
AlkOR<sup>10a</sup> [where Alk is a C<sub>1-3</sub>alkylene chain], -NR<sup>10a</sup>COR<sup>16</sup> [where R<sup>16</sup> is a C<sub>1-  
10 6</sub>alkyl group], -NR<sup>10a</sup>SO<sub>2</sub>R<sup>16</sup>, -SO<sub>2</sub>R<sup>16</sup>, -COR<sup>16</sup>, -CONR<sup>17</sup>R<sup>18</sup> [where R<sup>17</sup> and  
R<sup>18</sup>, which may be the same or different; is each a hydrogen atom or a C<sub>1-  
6</sub>alkyl group, or R<sup>17</sup> and R<sup>18</sup> may join together to form a 4 to 6 membered  
heterocycloalkyl group], -NR<sup>17</sup>R<sup>18</sup>, -SO<sub>2</sub>NR<sup>17</sup>R<sup>18</sup>, C<sub>1-6</sub>alkyl, haloC<sub>1-6</sub>alkyl or 5  
or 6 membered heteroaryl group.

- 15 16. A pharmaceutical composition comprising a compound according to  
any of Claims 1 to 14 together with one or more pharmaceutically acceptable  
carriers, excipients or diluents.
17. A compound according to any of Claims 1 to 14 for use in the treatment  
of cancer, inflammatory disorders, autoimmune disorders, psoriatic disorders  
20 and viral disorders.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB 03/03878

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D413/04 C07D239/70 C07D471/10 C07D487/10 C07D491/10  
A61K31/517 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

CHEM ABS Data, PAJ, WPI Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 14686 A (ASTRA) 24 April 1997 (1997-04-24) page 0; claims	1, 14, 16, 17

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

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- \*E\* earlier document but published on or after the International filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the International filing date but later than the priority date claimed

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Information on patent family members

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